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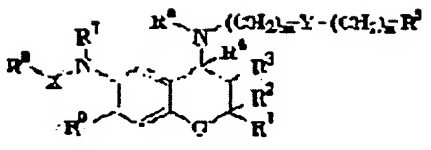
(54) BENZOPYRAN DERIVATIVE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a therapeutic agent for arrhythmia.

SOLUTION: This therapeutic agent for arrhythmia comprises a benzopyran derivative of formula (I) [R1 and R2 are each independently a 1-6C alkyl group or the like; R3 is a hydroxyl group or a 1-6C alkylcarbonyloxy group; R4 is a hydrogen atom or R3 and R4 are combined to form a bond; (m) is an integer of 0 to 4; (n) is an integer of 0 to 4; Y does not exist or CR11R12; R5 is an aryl group or a heteroaryl group; R6 is a hydrogen atom or a 1-6C alkyl group; R7 is a hydrogen atom or a 1-6C alkyl group; X does not exist or C=O or SO2: R8 is a 1-6C alkyl group or the like; and R9 is a nitro group or the like] or its



(I)

pharmaceutically permissible salt as an active ingredient.

LEGAL STATUS

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* NOTICES *

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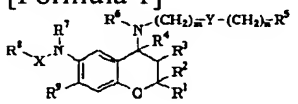
CLAIMS

[Claim(s)]
[Claim 1] Formula (I)
[Formula 1]



(I)

The inside of [type, and R1 and R2 become independent, respectively, and they are a hydrogen atom and C1-6 alkyl group (this alkyl group). the halogen atom, the C1-6 alkoxy group, or the hydroxyl group may permute with arbitration. Or a phenyl group (this phenyl group may be permuted by arbitration by a halogen atom, a hydroxyl group, the nitro group, the cyano group, the C1-6 alkyl group, or the C1-6 alkoxy group.) [whether it means and R3 means a hydroxyl group or a C1-6 alkylcarbonyloxy radical and] Or [whether it becomes together with R4, association is meant, and R4 means a hydrogen atom, and] Or it becomes together with R3, association is meant, m means the integer of 0-4, n means the integer of 0-4, and Y does not exist, or it is CR 11R12 (R11 and R12 mean independently a hydrogen atom or C1-6 alkyl group, respectively.). meaning -- R5 -- an aryl group or a hetero aryl group (each of these aryl groups and hetero aryl groups is q R10 (R10 -- a halogen atom --)) A hydroxyl group, C1-6 alkyl group (this alkyl group may be permuted by the halogen atom or the C1-6 alkoxy group), A nitro group, a cyano group, a formyl group, a formamide radical, the amino group, a C1-6 alkylamino radical, A JI C1-6 alkylamino radical, a C1-6 alkyl carbonylamino radical, A C1-6 alkyl sulfonylamino radical, an aminocarbonyl radical, a C1-6 alkylamino carbonyl group, a JI C1-6 alkylamino carbonyl group, a C1-6 alkyl carbonyl group, a C1-6 alkoxy carbonyl group, an amino sulfonyl group, a C1-6 alkyl sulfonyl group, a carboxyl group, or an aryl carbonyl group is meant. You may permute by arbitration. q expresses the integer of 1-3, and when q is 2 or 3, even if R10 is the same, it may differ. It means. R6 A hydrogen atom or C1-6 alkyl group is meant. R7 A hydrogen atom or C1-6 alkyl group is meant. X It does not exist or C=O or SO2 is meant. R8 meaning a hydrogen atom, C1-6 alkyl group (this alkyl group being permuted by the halogen atom, the hydroxyl group, or the C1-6 alkoxy group), or a C3-6 cycloalkyl radical, R9 means a hydrogen atom, a halogen atom, a nitro group, or a cyano group.] The benzopyran derivative which is alike and is expressed more, or its salt which may be permitted in physic.
[Claim 2] The benzopyran derivative according to claim 1 whose R3 is a hydroxyl group and whose R4 both R1 and R2 are methyl groups, and is a hydrogen atom, or its salt which may be permitted in physic.
[Claim 3] The benzopyran derivative according to claim 2 whose R9 is a hydrogen atom or a nitro group, or its salt which may be permitted in physic.
[Claim 4] The benzopyran derivative according to claim 3 whose X is C=O and both R6 and whose R7 are hydrogen atoms, or its salt which may be permitted in physic.
[Claim 5] They are the benzopyran derivative according to claim 4 whose m R5 is the benzene ring, and Y does not exist, but is 0 and whose n is 1 or 2, or its salt which may be permitted in physic.
[Claim 6] The benzopyran derivative according to claim 5 whose R8 is an alkyl group, whose R9 is a nitro group and whose n is 2, or its salt which may be permitted in physic.
[Claim 7] Physic characterized by containing a benzopyran derivative or its salt which may be

permitted in physic according to claim 1 as an active principle.
[Claim 8] The antiarrhythmic drug characterized by containing a benzopyran derivative or its salt which may be permitted in physic according to claim 1 as an active principle.

[Translation done.]

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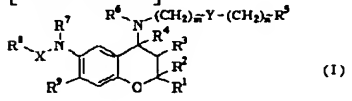
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention is used for the therapy of the arrhythmia to mammalian including Homo sapiens about the benzopyran derivative which has a refractory period extension operation.
[0002]
[Description of the Prior Art] 4-acylamino benzopyran derivative represented by chroma KARIMU (JP,58-67683,A) as a benzopyran derivative is known. Although 4-acylamino benzopyran derivative represented by these chroma KARIMU carries out opening of the ATP susceptibility K+ channel and it is known that it is effective in the therapy of hypertension or asthma, reference is not made about the therapy of arrhythmia based on a refractory period extension operation. By the way, the conventional antiarrhythmic drugs (for example, 1 **** of the antiarrhythmic drug classification by Vaughan Williams, d-sotalol belonging to three groups, etc.) which make a refractory period extension operation a main mechanism have are the technical problems on a therapy of a refractory period extension operation and the very dangerous arrhythmia induction operation which may induce sudden death, such as torsades de pointes based on extension of cardiac musculus ventricularis action potential with relation, and drugs with more few side effects are desire. In order that this invention persons might solve this technical problem, it found out that an atrium muscle had an alternative refractory period extension operation, without influencing the compound which does retrieval research of the compound which has an alternative refractory period extension operation in an atrium muscle, and is expressed with it by the general formula (I) rather than the cardiac musculus ventricularis at the refractory period and action potential of the cardiac musculus ventricularis.
[0003]
[Means for Solving the Problem] As a result of looking for a benzopyran derivative wholeheartedly, this invention persons have a refractory period extension operation strong against the compound expressed with a formula (I) to a surprising thing, found out that it was useful as an antiarrhythmic, and completed this invention.
[0004] This invention is a formula (I).
[0005]
[Formula 2]



(I)

[0006] The inside of [type, and R1 and R2 become independent, respectively, and they are a hydrogen atom and C1-6 alkyl group (this alkyl group). the halogen atom, the C1-6 alkoxy group, or the hydroxyl group may permute with arbitration. Or a phenyl group (this phenyl group may be permuted by arbitration by a halogen atom, a hydroxyl group, the nitro group, the cyano group, the C1-6 alkyl group, or the C1-6 alkoxy group.) [whether it means and R3 means a hydroxyl group or a C1-6 alkylcarbonyloxy radical and] Or [whether it becomes together with R4, association is meant, and R4 means a hydrogen atom, and] Or it becomes together with R3, association is meant, m means the integer of 0-4, n means the integer of 0-4, and Y does not exist, or it is CR 11R12 (R11

and R12 mean independently a hydrogen atom or C1-6 alkyl group, respectively.). meaning -- R5 -- an aryl group or a hetero aryl group (each of these aryl groups and hetero aryl groups is q R10 (R10 -- a halogen atom --)) A hydroxyl group, C1-6 alkyl group (this alkyl group may be permuted by the halogen atom or the C1-6 alkoxy group), A nitro group, a cyano group, a formyl group, a formamide radical, the amino group, a C1-6 alkylamino radical, A JI C1-6 alkylamino radical, a C1-6 alkyl carbonylamino radical, A C1-6 alkyl sulfonylamino radical, an aminocarbonyl radical, a C1-6 alkylamino carbonyl group, a JI C1-6 alkylamino carbonyl group, a C1-6 alkyl carbonyl group, a C1-6 alkoxy carbonyl group, an amino sulfonyl group, a C1-6 alkyl sulfonyl group, a carboxyl group, or an aryl carbonyl group is meant. You may permute by arbitration. q expresses the integer of 1-3, and when q is 2 or 3, even if R10 is the same, it may differ. It means. R6 A hydrogen atom or C1-6 alkyl group is meant. R7 A hydrogen atom or C1-6 alkyl group is meant. X It does not exist or C=O or SO2 is meant. R8 meaning a hydrogen atom, C1-6 alkyl group (this alkyl group being permuted by the halogen atom, the hydroxyl group, or the C1-6 alkoxy group), or a C3-6 cycloalkyl radical, R9 means a hydrogen atom, a halogen atom, a nitro group, or a cyano group.] It is related with the benzopyran derivative which is alike and is expressed more, or its salt which may be permitted in physic.

[0007] this invention compound has a strong refractory period extension operation, and it can be used for it as an antiarrhythmic drug.

[0008] Next, each substituent of this invention compound (I) is explained concretely. in addition, this detail in the letter "n" -- normal -- "i" -- ISO -- "s" -- SEKANDARI -- "t" -- tertiary -- "c" -- cyclo -- in "o", "m" means meta and "p" means Para for ORUTO.

[0009] As C1-6 alkyl group, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neopentyl, 2, and 2-dimethyl propyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-n-pentyl, 1, 1, 2-trimethyl-n-propyl, 1 and 2, and 2-trimethyl-n-propyl, 3, and 3-dimethyl-n-butyl, trifluoromethyl, trifluoro ethyl, pentafluoro ethyl, cyano methyl, hydroxymethyl, etc. are mentioned. Preferably, methyl, ethyl, n-propyl, i-propyl, and n-butyl are mentioned.

[0010] As a halogen atom, a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom are mentioned. Preferably, a fluorine atom, a chlorine atom, and a bromine atom are mentioned.

[0011] As C1-6 alkoxy group, methoxy, trifluoro methoxy, Ethoxy **n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, 1-pentyloxy, 2-pentyloxy, 3-pentyloxy, i-pentyloxy, neopentyl oxy-**2, and 2-dimethyl propoxy, 1-hexyloxy, 2-hexyloxy, 3-hexyloxy, 1-methyl-n-pentyloxy, 1 and 1, 2-trimethyl-n-propoxy, 1 and 2, and 2-trimethyl-n-propoxy and 3, and 3-dimethyl-n-butoxy etc. is mentioned. Preferably, methoxy and ethoxy **n-propoxy and i-propoxy are mentioned.

[0012] As a C1-6 alkylcarbonyloxy radical Methyl carbonyloxy, ethyl carbonyloxy, n-propyl carbonyloxy, i-propyl carbonyloxy, n-butyl carbonyloxy, i-butyl carbonyloxy, s-butyl carbonyloxy, t-butyl carbonyloxy, 1-pentyl carbonyloxy, 2-pentyl carbonyloxy, 3-pentyl carbonyloxy, i-pentyl carbonyloxy, Neopentyl carbonyloxy, t-pentyl carbonyloxy, 1-hexyl carbonyloxy, 2-hexyl carbonyloxy, 3-hexyl carbonyloxy, 1-methyl-n-pentyl carbonyloxy, 1, 1, 2-trimethyl-n-propyl carbonyloxy, 1 and 2, and 2-trimethyl-n-propyl carbonyloxy and 3, and 3-dimethyl-n-butyl carbonyloxy etc. is mentioned. Preferably, methyl carbonyloxy, ethyl carbonyloxy, n-propyl carbonyloxy, i-propyl carbonyloxy, n-butyl carbonyloxy, and t-butyl carbonyloxy are mentioned.

[0013] As an aryl group, phenyl, biphenylyl, naphthyl, anthryl, phenan tolyl, etc. are mentioned. Preferably, phenyl, biphenylyl, and naphthyl are mentioned.

[0014] As a hetero aryl group, 2-thienyl group, 3-thienyl group, 2-furil radical, 3-furil radical, 2-pyranyl radical, 3-pyranyl radical, 4-pyranyl radical, A 2-benzofuranyl radical, a 3-benzofuranyl radical, a 4-benzofuranyl radical, A 5-benzofuranyl radical, a 6-benzofuranyl radical, a 7-benzofuranyl radical, A 1-iso benzofuranyl radical, a 4-iso benzofuranyl radical, a 5-iso benzofuranyl radical, 2-benzothienyl group, 3-benzothienyl group, 4-benzothienyl group, 5-benzothienyl group, 6-benzothienyl group, 7-benzothienyl group, A 1-iso benzothienyl group, a 4-iso benzothienyl group, a 5-iso benzothienyl group, 2-clo MENIRU radical, 3-clo MENIRU radical, 4-clo MENIRU radical, 5-clo MENIRU radical, 6-clo MENIRU radical, 7-clo MENIRU radical, 8-clo MENIRU radical, 1-pyrrolyl radical, 2-pyrrolyl radical, 3-pyrrolyl radical, 1-imidazolyl radical, 2-imidazolyl radical, 4-imidazolyl radical, 1-pyrazolyl radical, 3-pyrazolyl radical, 4-pyrazolyl radical, 2-thiazolyl radical, 4-thiazolyl radical, 5-thiazolyl radical, a 3-iso thiazolyl radical, A 4-iso

thiazolyl radical, a 5-iso thiazolyl radical, 2-oxazolyl radical, 4-oxazolyl radical, 5-oxazolyl radical, a 3-iso oxazolyl radical, A 4-iso oxazolyl radical, a 5-iso oxazolyl radical, 2-pyridyl radical, 3-pyridyl radical, 4-pyridyl radical, a 2-pyrazinyl radical, 2-pyrimidinyl group, 4-pyrimidinyl group, 5-pyrimidinyl group, 3-pilus DAJINIRU radical, 4-pilus DAJINIRU radical, 1-in DORIJINIRU radical, 2-in DORIJINIRU radical, 3-in DORIJINIRU radical, 5-in DORIJINIRU radical, 6-in DORIJINIRU radical, 7-in DORIJINIRU radical, 8-in DORIJINIRU radical, a 1-iso indolyl radical, a 4-iso indolyl radical, A 5-iso indolyl radical, 1-indolyl radical, 2-indolyl radical, 3-indolyl radical, 4-indolyl radical, 5-indolyl radical, 6-indolyl radical, 7-indolyl radical, 1-indazolyl group, 2-indazolyl group, 3-indazolyl group, 4-indazolyl group, 5-indazolyl group, 6-indazolyl group, 7-indazolyl group, 1-Puri Nils radical, 2-Puri Nils radical, 3-Puri Nils radical, 6-Puri Nils radical, 7-Puri Nils radical, 8-Puri Nils radical, 2-quinolyl radical, 3-quinolyl radical, 4-quinolyl radical, 5-quinolyl radical, 6-quinolyl radical, 7-quinolyl radical, 8-quinolyl radical, A 1-iso quinolyl radical, a 3-iso quinolyl radical, a 4-iso quinolyl radical, a 5-iso quinolyl radical, A 6-iso quinolyl radical, a 7-iso quinolyl radical, a 8-iso quinolyl radical, a 1-phthalazinyl radical, 5-phthalazinyl radical, 6-phthalazinyl radical, 2-naphthyridinyl group, 3-naphthyridinyl group, 4-naphthyridinyl group, 2-kino KISARINIRU radical, 5-kino KISARINIRU radical, 6-kino KISARINIRU radical, 2-chinae-cortex ZORINIRU radical, 4-chinae-cortex ZORINIRU radical, 5-chinae-cortex ZORINIRU radical, 6-chinae-cortex ZORINIRU radical, 7-chinae-cortex ZORINIRU radical, 8-chinae-cortex ZORINIRU radical, 3-SHINNORINIRU radical, 4-SHINNORINIRU radical, 5-SHINNORINIRU radical, 6-SHINNORINIRU radical, 7-SHINNORINIRU radical, 8-SHINNORINIRU radical, 2-PUTENIJINIRU radical, 4-PUTENIJINIRU radical, 6-PUTENIJINIRU radical, 7-PUTENIJINIRU radical, 3-furazanyl group, etc. are mentioned. Preferably, 2-pyridyl radical, 3-pyridyl, and a radical 4-pyridyl radical are mentioned.

[0015] As a C1-6 alkylamino radical, methylamino, ethylamino, n-propylamino, i-propylamino, c-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, c-butylamino, 1-pentylamino, 2-pentylamino, 3-pentylamino, i-pentylamino, Neopentyl amino, t-pentylamino, c-pentylamino, 1-hexylamino, 2-hexylamino, 3-hexylamino, c-hexylamino, 1-methyl-n-pentylamino, 1 and 1, 2-trimethyl-n-propylamino, 1 and 2, and 2-trimethyl-n-propylamino and 3, and 3-dimethyl-n-butylamino etc. is mentioned. Preferably, methylamino, ethylamino, n-propylamino, i-propylamino, and n-butylamino are mentioned.

[0016] As a JI C1-6 alkylamino radical, dimethylamino, diethylamino, G n-propylamino, G i-propylamino, G c-propylamino, G n-butylamino, G i-butylamino, G s-butylamino, G t-butylamino, G c-butylamino, G 1-pentylamino, G 2-pentylamino, G 3-pentylamino, G i-pentylamino, G neopentyl amino, G t-pentylamino, G c-pentylamino, G 1-hexylamino, G 2-hexylamino, G 3-hexylamino, G c-hexylamino, G (1-methyl-n-pentyl) amino, G (1, 1, 2-trimethyl-n-propyl) amino, G (1, 2, and 2-trimethyl-n-propyl) amino, G (3 and 3-dimethyl-n-butyl) amino, methyl (ethyl) amino, Methyl (n-propyl) amino, methyl (i-propyl) amino, methyl (c-propyl) amino, Methyl (n-butyl) amino, methyl (i-butyl) amino, methyl (s-butyl) amino, Methyl (t-butyl) amino, methyl (c-butyl) amino, ethyl (n-propyl) amino, Ethyl (i-propyl) amino, ethyl (c-propyl) amino, ethyl (n-butyl) amino, Ethyl (i-butyl) amino, ethyl (s-butyl) amino, ethyl (t-butyl) amino, Ethyl (c-butyl) amino, n-propyl (i-propyl) amino, n-propyl (c-propyl) amino, n-propyl (n-butyl) amino, n-propyl (i-butyl) amino, n-propyl (s-butyl) amino, n-propyl (t-butyl) amino, n-propyl (c-butyl) amino, i-propyl (c-propyl) amino, i-propyl (n-butyl) amino, i-propyl (i-butyl) amino, i-propyl (s-butyl) amino, i-propyl (t-butyl) amino, i-propyl (c-butyl) amino, c-propyl (n-butyl) amino, c-propyl (i-butyl) amino, c-propyl (s-butyl) amino, c-propyl (t-butyl) amino, c-propyl (c-butyl) amino, n-butyl (i-butyl) amino, n-butyl (s-butyl) amino, n-butyl (t-butyl) amino, n-butyl (c-butyl) amino, i-butyl (s-butyl) amino, i-butyl (t-butyl) amino, i-butyl (c-butyl) amino, s-butyl (t-butyl) amino, s-butyl (c-butyl) amino, t-butyl (c-butyl) amino, etc. are mentioned. Preferably, dimethylamino, diethylamino, G n-propylamino, G i-propylamino, and G n-butylamino are mentioned.

[0017] As a C1-6 alkyl carbonylamino radical Methyl carbonylamino, ethyl carbonylamino, n-propyl carbonylamino, i-propyl carbonylamino, n-butyl carbonylamino, i-butyl carbonylamino, s-butyl carbonylamino, t-butyl carbonylamino, 1-pentyl carbonylamino, 2-pentyl carbonylamino, 3-pentyl carbonylamino, i-pentyl carbonylamino, Neopentyl carbonylamino, t-pentyl carbonylamino, 1-hexyl carbonylamino, 2-hexyl carbonylamino, 3-hexyl carbonylamino, etc. are mentioned. Preferably,

methyl carbonylamino, ethyl carbonylamino, n-propyl carbonylamino, i-propyl carbonylamino, and n-butyl carbonylamino are mentioned.
[0018] As a C1-6 alkyl sulfonylamino radical Methylsulfonylamino, ethyl sulfonylamino, n-propyl sulfonylamino, i-propyl sulfonylamino, n-butylsulphonylamino, i-butylsulphonylamino, s-butylsulphonylamino, t-butylsulphonylamino, 1-pentyl sulfonylamino, 2-pentyl sulfonylamino, 3-pentyl sulfonylamino, i-pentyl sulfonylamino, Neopentyl sulfonylamino, t-pentyl sulfonylamino, 1-hexyl sulfonylamino, 2-hexyl sulfonylamino, 3-hexyl sulfonylamino, etc. are mentioned. Preferably, methylsulfonylamino, ethyl sulfonylamino, n-propyl sulfonylamino, i-propyl sulfonylamino, and n-butylsulphonylamino are mentioned.
[0019] As a C1-6 alkylamino carbonyl group Methylamino carbonyl, ethylamino carbonyl, n-propylamino carbonyl, i-propylamino carbonyl, n-butylamino carbonyl, i-butylamino carbonyl, s-butylamino carbonyl, t-butylamino carbonyl, 1-pentylamino carbonyl, 2-pentylamino carbonyl, 3-pentylamino carbonyl, i-pentylamino carbonyl, Neopentyl aminocarbonyl, t-pentylamino carbonyl, 1-hexylamino carbonyl, 2-hexylamino carbonyl, 3-hexylamino carbonyl, etc. are mentioned. Preferably, methylamino carbonyl, ethylamino carbonyl, n-propylamino carbonyl, i-propylamino carbonyl, and n-butylamino carbonyl are mentioned.
[0020] As a JI C1-6 alkylamino carbonyl group Dimethylamino carbonyl, diethylamino carbonyl, G n-propylamino carbonyl, G i-propylamino carbonyl, G c-propylamino carbonyl, G n-butylamino carbonyl, G i-butylamino carbonyl, G s-butylamino carbonyl, G t-butylamino carbonyl, G c-butylamino carbonyl, G 1-pentylamino carbonyl, G 2-pentylamino carbonyl, G 3-pentylamino carbonyl, G i-pentylamino carbonyl, G neopentyl aminocarbonyl, G t-pentylamino carbonyl, G c-pentylamino carbonyl, G 1-hexylamino carbonyl, G 2-hexylamino carbonyl, G 3-hexylamino carbonyl, etc. are mentioned. Preferably, dimethylamino carbonyl, diethylamino carbonyl, G n-propylamino carbonyl, G i-propylamino carbonyl, G c-propylamino carbonyl, and G n-butylamino carbonyl are mentioned.
[0021] As a C1-6 alkyl carbonyl group, methyl carbonyl, ethyl carbonyl, n-propylcarbonyl, i-propylcarbonyl, n-butyl carbonyl, i-butyl carbonyl, s-butyl carbonyl, t-butyl carbonyl, 1-pentyl carbonyl, 2-pentyl carbonyl, 3-pentyl carbonyl, i-pentyl carbonyl, neopentyl carbonyl, t-pentyl carbonyl, 1-hexyl carbonyl, 2-hexyl carbonyl, and 3-hexyl carbonyl are mentioned. Preferably, methyl carbonyl, ethyl carbonyl, n-propylcarbonyl, i-propylcarbonyl, and n-butyl carbonyl are mentioned.
[0022] As a C1-6 alkoxy carbonyl group, methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, i-propoxy carbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl, 1-pentyloxy carbonyl, 2-pentyloxy carbonyl, 3-pentyloxy carbonyl, i-pentyloxy carbonyl, neopentyl oxy-carbonyl, t-pentyloxy carbonyl, 1-hexyloxy carbonyl, 2-hexyloxy carbonyl, 3-hexyloxy carbonyl, etc. are mentioned. Preferably, methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, i-propoxy carbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, and t-butoxycarbonyl are mentioned.
[0023] A methane sulfonyl and an ethane sulfonyl are mentioned as a C1-6 alkyl sulfonyl group.
[0024] As an aryl carbonyl group, benzoyl, p-methyl benzoyl, p-t-butyl benzoyl, p-methoxy benzoyl, p-KURORU benzoyl, p-nitrobenzoyl, and p-cyano benzoyl are mentioned. Preferably, benzoyl, p-nitrobenzoyl, and p-cyano benzoyl are mentioned.
[0025] As a C3-6 cycloalkyl radical, cyclo propyl, cyclo butyl, cyclopentyl, cyclohexyl, cycloheptyl one, cyclo octyl, etc. are mentioned. Preferably, cyclo propyl, cyclo butyl, and cyclohexyl are mentioned.
[0026] The compound shown below is mentioned as a desirable compound used for this invention.
[0027] (1) The benzopyran derivative expressed with the formula (I) whose R3 is a hydroxyl group, and whose R4 both R1 and R2 are methyl groups, and is a hydrogen atom, or its salt which may be permitted in physic.
[0028] (2) The benzopyran derivative or its salt which may be permitted in physic of the above-mentioned (1) publication whose R9 is a hydrogen atom or a nitro group.
[0029] (3) The benzopyran derivative or its salt which may be permitted in physic of the above-mentioned (2) publication whose X is C=O and both R6 and whose R7 are hydrogen atoms.
[0030] (4) R5 is the benzene ring, Y does not exist, but m is 0 and n is 1 or 2 -- coming out -- a

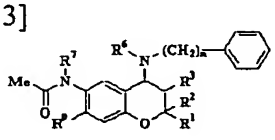
benzopyran derivative given in above-mentioned [a certain] (3), or its salt which may be permitted in physic.

[0031] (5) The benzopyran derivative or its salt which may be permitted in physic of the above-mentioned (4) publication whose R8 is an alkyl group, whose R9 is a nitro group and whose n is 2.

[0032] Although the example of the compound which can be used for this invention is shown below, this invention is not restricted to these. In addition, "Ac" means an acetyl group (COCH3) and, as for "-", ", for "Et", "Pr" is [Me" / methyl group] "Bu about a propyl group in an ethyl group" means association for butyl, respectively.

[0033]

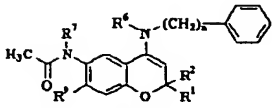
[Formula 3]



R^1	R^2	R^3	R^8	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	3
Me	Me	OH	H	H	NO_2	4
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

[0034]

[Formula 4]



R^1	R^2	R^8	R^7	R^9	n
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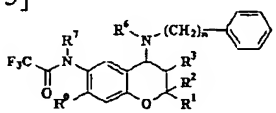
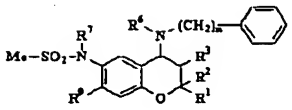
Me	Me	Me	H	H	1
Me	Me	Et	H	H	2
Me	Me	n-Pr	H	H	3
Me	Me	i-Pr	H	H	4
Me	Me	n-Bu	H	H	0
Me	Me	i-Bu	H	H	1
Me	Me	t-Bu	H	H	2
Me	Me	n-Pen	H	H	3
Me	Me	n-Hex	H	H	4
Me	Me	H	H	H	2
Me	Me	Me	H	H	2
Me	Me	Et	H	H	3
Me	Me	H	H	H	2
Me	Me	H	H	NO_2	2
Me	Me	H	Me	NO_2	1
Me	Me	H	Et	NO_2	2
Me	Me	H	n-Pr	NO_2	3
Ph	Ph	H	i-Pr	NO_2	4
Et	Et	H	n-Bu	NO_2	2
n-Pr	n-Pr	H	i-Bu	NO_2	2
i-Pr	i-Pr	H	t-Bu	NO_2	2
n-Bu	n-Bu	H	n-Pen	NO_2	2
i-Bu	i-Bu	H	n-Hex	NO_2	2
t-Bu	t-Bu	H	Me	NO_2	3
n-Pen	n-Pen	H	H	Cl	3
n-Hex	n-Hex	H	H	F	3
CF_3	CF_3	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	H	H	CN	3

[0035]
[Formula 5]



R^1	R^2	R^3	R^6	R^7	R^8	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

[0036]
[Formula 6]



R^1	R^2	R^3	R^6	R^7	R^9	n
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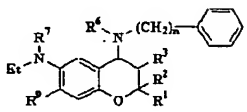
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

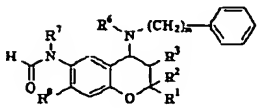
[0037]



R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

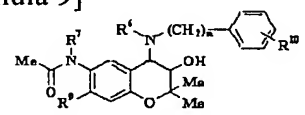
[Formula 7]

[0038]
[Formula 8]



R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

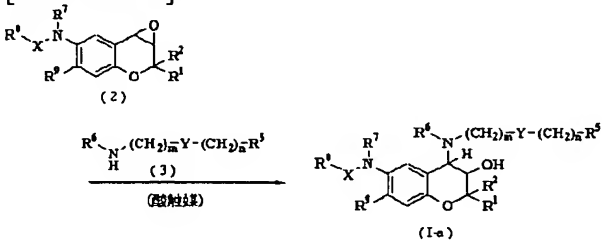
[0039]
[Formula 9]



R^6	R^7	R^9	R^{10}	n
H	H	H	p-MeO	0
Me	H	H	p-MeO	1
H	H	NO_2	p-MeO	2
n-Pr	H	H	p-MeO	3
i-Pr	H	H	p-MeO	4
n-Bu	H	H	m-MeO	0
i-Bu	H	H	o-MeO	1
t-Bu	H	H	p-Me	2
n-Pen	H	H	p-Et	3
n-Hex	H	H	m-Et	4
H	H	H	o-Et	2
H	H	NO_2	p-Cl	2
Et	H	H	p-F	3
H	H	NO_2	p-OH	2
H	H	NO_2	p-OH	2
H	Me	NO_2	p-NO_2	1
H	Et	NO_2	p-CN	2
H	n-Pr	NO_2	p-NMe_2	3
H	i-Pr	NO_2	p-NHMe	4
H	n-Bu	NO_2	p-CO_2H	2
H	i-Bu	NO_2	m-CO_2Et	2
H	t-Bu	NO_2	m-OMe	2
H	H	NO_2	p-NO_2	2
H	n-Hex	NO_2	p-NMe_2	2
H	Me	NO_2	p-NHMe	3
H	H	NO_2	p-NH_2	2
H	H	F	p-Et	3
H	H	Br	p-Pr	3
H	H	CN	p-CH_2OMe	3

[0040] Although this invention compound has asymmetrical carbon in the 3rd place and the 4th place and the optical isomer based on this asymmetrical carbon exists, the optically active substance as well as racemic modification can be used for the application of this invention. Moreover, although cis- ** based on the configuration of the 3rd place and the 4th place also includes a trans isomer, it is a trans isomer preferably.

[0041] Moreover, when it is the compound which can form a salt, the salt which can be permitted in physic can also be used as an active principle. As a salt which can be permitted in physic, a hydrochloride, the hydrobromate, a sulfate, a methansulfonic acid salt, acetate, a benzoate, a tartrate, phosphate, a lactate, a maleate, a fumaric-acid salt, malate, gluconate, salicylate, etc. are mentioned. Preferably, a hydrochloride and a methansulfonic acid salt are mentioned.
[0042]
[Embodiment of the Invention]
[0043] Next, the process of this invention compound is explained.
[0044] R4 is a hydrogen atom among the compounds expressed by the general formula (I), and the compound whose R3 is a hydroxyl group and which is expressed with (I-a) can be obtained by making the compound and compound (3) which are expressed by the general formula (2) react among an inert solvent, as shown in the following reaction formula. the compound expressed by the general formula (2) -- a known approach (J.M.Evans et al. --) J.Med.Chem.1984, 27, 1127, J.Med.Chem.1986, 29, 2194, J.T.North et al. -- J.Org.Chem.1995, 60, and 3397 -- According to the approach of a publication, it is compoundable to JP,56-57785,A, JP,56-57786,A, JP,58-188880,A, JP,2-141,A, JP,10-87650,A public relations, JP,11-209366,A public relations, etc.
[0045]
[Formula 10]



[0046] The following are mentioned as a solvent used for the reaction of the compound and compound (3) which are expressed by the general formula (2). The amide system solvent represented by the sulfoxide system solvent, dimethylformamide, or dimethylacetamide represented with dimethyl sulfoxide, The ether system solvent represented by ethyl ether, dimethoxyethane, or the tetrahydrofuran, Dichloromethane, chloroform, the halogen system solvent represented by the dichloroethane, The hydrocarbon system solvent represented by the nitril system solvent represented by an acetonitrile and propionitrile, benzene, the aromatic hydrocarbon system solvent represented by toluene, the hexane, and the heptane and the ester solvent represented with ethyl acetate are mentioned. Moreover, it can also react on condition that a non-solvent. An ether system solvent and a nitril system solvent are mentioned preferably.
[0047] Reaction temperature is to the reflux temperature of the reaction solvent usually used from -80 degrees C, and is -10 degrees C - 100 degrees C preferably.
[0048] The range of compound (3) / compound (2) is 0.5-20.0, and the range of the mole ratio of a reaction raw material is 1.0-10.0 preferably.
[0049] An acid catalyst may be used for a reaction.
[0050] The Lewis acid represented by a hydrochloric acid, the inorganic acid represented by the sulfuric acid, an aluminum chloride, a titanium tetrachloride, a boron-trifluoride diethylether complex, perchloric acid, lithium perchlorate, a lithium bromide, and the trifluoro methansulfonic acid ytterbium as an acid catalyst to be used is mentioned.
[0051] Preferably, a lithium bromide, perchloric acid, and lithium perchlorate are mentioned.
[0052] What is not contained in the compound expressed with (I-a) among the compounds expressed by the general formula (I) (compound the compound with which R3 and R4 become together, and they mean association, and whose R4 are hydrogen atoms and whose R3 is a C1-6 alkylcarbonyloxy radical) can be manufactured by the manufacturing method of a publication, and the same approach to JP,52-91866,A, JP,10-87650,A, etc.
[0053] Composition of the optically active substance is attained among the compounds expressed by the general formula (I) by using the approach (JP,3-141286,A, a U.S. Pat. No. 5097037 number, and Europe JP,409165,B) of carrying out optical resolution of the racemic modification. Moreover,

composition of the optically active substance of the compound expressed by the general formula (2) is attained by using the approach (the Patent Publication Heisei No. 507645 [five to] official report, JP,5-301878,A, JP,7-285983,A, the Europe JP,535377,B public presentation official report, and U.S. Pat. No. 5420314 number) by the asymmetric synthesis.

[0054] As mentioned above, this invention persons found out having the refractory period extension operation strong against the compound expressed with a general formula (I). A refractory period extension operation is one of the success mechanisms of an antiarrhythmic action, and is the important index which can extrapolate the effectiveness over clinical arrhythmia. The conventional antiarrhythmic drugs (for example, d-sotalol belonging to the 3rd group of the antiarrhythmic drug classification by Vaughan Williams etc.) which make a refractory period extension operation a main mechanism are made into the technical problem with serious refractory period extension operation and very dangerous arrhythmia induction operation which may induce sudden death, such as torsades de pointes based on extension of cardiac musculus-ventricularis action potential with relation, and an atrium muscle has been the problem of a therapy over a subject's arrhythmia (supraventricular ******, auricular flutter, atrial fibrillation, etc.). It found out that an atrium muscle had an alternative refractory period extension operation, without influencing the compound which this invention persons do retrieval research of the compound which has an alternative refractory period extension operation in an atrium muscle rather than the cardiac musculus ventricularis, and is expressed by the general formula (I) at the refractory period and action potential of the cardiac musculus ventricularis, in order to solve this technical problem. The difference from the existing technique of discovery of this invention persons is in the place which could give the alternative refractory period extension operation to the atrium muscle to these compound groups, and this is shown by not influencing the action potential persistence time of the extracted cardiac musculus ventricularis, and by not affecting the electrocardiogram QT of an anesthesia animal. From the above thing, this compound does not have the arrhythmia induction operation in the cardiac musculus ventricularis with it, but possibility that an atrium muscle can contribute to safer use in a subject's arrhythmia compared with the existing technique can be offered. This technique is useful as a purpose of prevention of the vital-prognosis aggravation based on the atrial arrhythmia or the tachycardia prevention operation which may shift to prevention, the ventricular arrhythmia, or the tachycardia of the shift to the ventricular arrhythmia or the tachycardia which considers the therapy or the prophylactic use, the progress prevention to the embolism based on atrial arrhythmia, atrial arrhythmia, or tachycardia as the antifibrillatory agent under [before fitfulness, chronic, and an operation] operation or after an operation, an anti-auricular-flutter agent, and an anti-atrial-tachycardia agent as a cause with respect to atrial arrhythmia.

[0055] This invention offers the physic constituent or veterinarian medicine constituent containing the effective amount of the compound expressed with a general formula (I) to these therapies.

[0056] As an administration gestalt of the compound concerning this invention, internal use by the parenteral administration by injections (the inside of hypodermically and a vein, intramuscular, intraperitoneal injection), the ointment, suppositories, aerosols, etc. or a tablet, a capsule, a granule, a pill, syrups, liquids and solutions, the emulsion, a suspension agent, etc. can be raised.

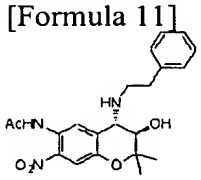
[0057] A veterinarian medicine-constituent contains about 0.1 - 30% for the compound concerning this invention with the above containing the compound concerning this invention like physic or preferably about 0.01 to 99.5% to the weight of all constituents.

[0058] the compound concerning this invention -- or the constituent containing this compound -- in addition, a compound [activity / in veterinarian medicine / like other physic or] can be included. Moreover, these constituents can include the plurality of the compound concerning this invention.

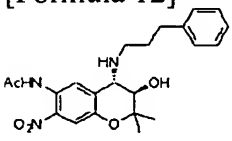
[0059] Although the clinical dose of this invention compound changes with age, weight, a patient's susceptibility, extent of a symptom, etc., a usually effective dose is about 0.01-0.6g preferably 0.003-1.5g of adult days. However, the above-mentioned amount out of range can also be used as occasion demands.

[0060] this invention compound is pharmaceutical-preparation-ized for administration by the common use means of medicine manufacture. Namely, the tablet for internal use, a capsule, a granule, and a pill An excipient, for example, white soft sugar, a lactose, grape sugar, starch, mannite; A binder, For example, hydroxypropylcellulose, syrup, gum arabic, gelatin, Sorbitol,

tragacanth, methyl cellulose, a polyvinyl pyrrolidone; Disintegrator, For example, starch, a carboxymethyl cellulose, or its calcium salt, A microcrystal cellulose, polyethylene-glycol; lubricant, for example, talc, magnesium stearate or calcium, a silica; it is prepared using lubricant, for example, lauryl acid sodium, glycerol, etc.
[0061] Injections, liquids and solutions, an emulsion, suspension, syrups, and aerosols The solvent of an active ingredient, for example, water, ethyl alcohol, isopropyl alcohol, Propylene glycol, 1, 3-butylene glycol, a polyethylene glycol; A surfactant, For example, a sorbitan fatty acid ester, polyoxyethylene sorbitan fatty acid ester, Polyoxyethylene fatty acid ester, the polyoxyethylene ether of hydrogenation castor oil, Lecithin; it is prepared using the ester of natural rubber; preservatives, for example, parahydroxybenzoic acid, such as cellulosics, such as suspension, for example, carboxymethyl sodium salt, and methyl cellulose, tragacanth, and gum arabic, a benzalkonium chloride, a sorbic-acid salt, etc.
[0062] White vaseline, a liquid paraffin, higher alcohol, macrogol ointment, hydrophilic ointment, an aquosity gel basis, etc. are used for the ointment which is percutaneous absorption mold pharmaceutical preparation. Suppositories are prepared using cacao butter, a polyethylene glycol, lanolin, fatty-acid triglyceride, a coconut oil, polysorbate, etc.
[0063]
[Example] Hereafter, although this invention is explained in full detail in the example, this invention is not limited to these examples at all.
[A synthetic example]
[0064] Synthetic example 1 transformer-6-acetylamino -3, 4-dihydro - 2 2-dimethyl-7-nitro-4-(2-phenethyl amino)-2H-1-benzopyran-3-all [0065]
[Formula 11]

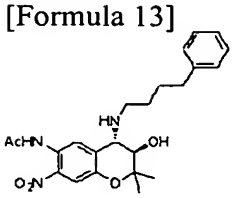


[0066] 6-acetylamino -3, 4-epoxy -3, 4-dihydro-2, and 2-dimethyl-7-nitro-2H-1-benzopyran (500 mg, 1.80 mmol) Lithium perchlorate (766mg, 7.20 mmol) ** tetrahydrofuran solution (15 mL) At a room temperature 2-phenethylamine (904 muL, 7.20 mmol) It is at 65 ** moreover. 9 Time amount churning was carried out. Ethyl acetate was added, saturation brine washed the organic phase once twice by the saturated ammonium chloride solution, and it dried with sulfuric anhydride magnesium. It is a medium-voltage column chromatography about the residue after distilling off a solvent. (hexane : ethyl acetate = 1: one) After refining, it recrystallized with hexane-ethyl acetate and the specified substance was obtained as a yellow crystal (yield 61 %).
[0067] mp. : 172-174 **C1 H-NMR delta (CDCl3): 1.17 (s, 3H), 1.48 (s, 3H) and 1.60 (br s, 2H), 2.28 (s, 3H) and 2.83 (t and J = 7.0 Hz, 2H), 2.85-3.00 (m, 2H) and 3.47 (d, A part of AB, J = 10.3 Hz, 1H), 3.67 (d, B part of AB, J = 10.3 Hz, 1H), 7.21-7.33 (m, 5H), 7.60 (s, 1H), 8.59 (s, 1H), and 9.96.(s, 1H) MS (EI) m/z; 400 [M+1] +327 (bp) . [0068] The following compound was obtained by the same approach. (Synthetic examples 2-36)
[0069] Synthetic example 2 transformer-6-acetylamino -3, 4-dihydro - 2 2-dimethyl-7-nitro-4-(3-phenylpropylamino)-2H-1-benzopyran-3-all [0070]
[Formula 12]

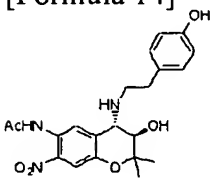


[0071] Yield 71 %1 H-NMR delta (CDCl3):1.21 (s, 3H), 1.51 (s, 3H) and 1.87 (quint, J = 7.4 Hz, 2H), 1.94 (br s, 2H) and 2.27 (s, 3H), 2.63-2.73 (m, 4H) and 3.54 (d, A part ofAB, J = 10.3 Hz, 1H), 3.71 (d, B part of AB, J = 10.3 Hz, 1H), 7.16-7.23 (m, 3H), 7.25-7.27 (m, 2H), 7.63 (s, 1H), 8.68 (s, 1H), and 10.02.(s, 1H) MS (EI) m/z; 413 [M] +221 (bp) . [0072] Synthetic example 3 transformer-6-acetylamino -3, 4-dihydro - 2 2-dimethyl-7-nitro-4-(4-phenyl butylamino)-2H-1-benzopyran-3-all

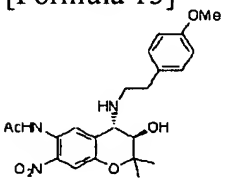
[0073]
[Formula 13]



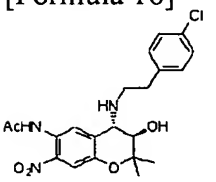
[0074] Yield 50 %1 H-NMR delta (CDCl3):1.20 (s, 3H), 1.52 (s, 3H) and 1.55-1.60 (m, 2H), 1.63-1.75 (m, 2H) and 2.25 (s, 3H), 2.40 (br s, 2H) and 2.62 (t and J = 7.4 Hz, 2H), 2.58-2.72 (m, 2H) and 3.57 (d, A part of AB, J = 10.0 Hz, 1H), 3.70 (d, B partof AB, J = 10.0 Hz, 1H), 7.15-7.18 (m, 3H), 7.24-7.62 (m, 2H), 7.62 (s, 1H), 8.67 (s, 1H), and 10.00.(s, 1H) MS (EI) m/z; 427 [M] +150 (bp) . [0075] synthetic example 4 transformer-6-acetylamino -3, 4-dihydro-2, and 2-dimethyl-7-nitro-4- [2-(4-hydroxyphenyl) ethylamino]-2H-1-benzopyran-3-oar [0076]
[Formula 14]



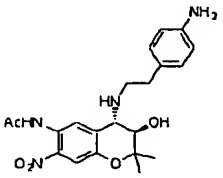
[0077] Yield 29 %1 H-NMR delta (CDCl3):1.17 (s, 3H), 1.48 (s, 3H) and 2.00 (br s, 3H), 2.29 (s, 3H) and 2.70-2.85 (m, 3H), 2.86-2.95 (m, 1H) and 3.51 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, B part of AB, J = 10.3 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H) and 7.06 (d and J = 8.4 Hz, 2H), 7.60 (s, 1H), 8.46 (s, 1H), and 9.95(s, 1H).MS (EI) m/z; 416 [M+1] +308 (bp) . [0078] synthetic example 5 transformer-6-acetylamino -3, 4-dihydro-2, and 2-dimethyl-7-nitro-4- [2-(4-methoxypheny) ethylamino]-2H-1-benzopyran-3-oar [0079]
[Formula 15]



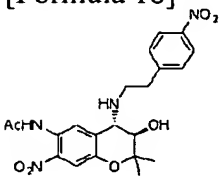
[0080] Yield 18 %1 H-NMR delta (CDCl3):1.18 (s, 3H), 1.49 (s, 3H) and 1.80 (br s, 2H), 2.27 (s, 3H) and 2.76-3.00 (m, 4H), 3.56 (d, A part of AB, J = 10.5 Hz, 1H), 3.77 (d, B part of AB, J = 10.5 Hz, 1H), 3.79 (s, 3H) and 6.83 (d and J = 8.6 Hz, 2H), 7.23 (d and J = 8.6 Hz, 2H), 7.61 (s, 1H), 8.55 (s, 1H), and 9.93 (s, 1H).MS (EI) m/z; 430 [M+1] + (bp) . [0081] synthetic example 6 transformer-6-acetylamino -3, 4-dihydro-2, and 2-dimethyl-7-nitro-4- [2-(4-chlorophenyl) ethylamino]-2H-1-benzopyran-3-oar [0082]
[Formula 16]



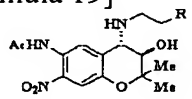
[0083] Yield 66 %1 H-NMR delta (CDCl3):1.18 (s, 3H), 1.49 (s, 3H) and 1.70 (br s, 2H), 2.28 (s, 3H) and 2.78 (t and J = 6.8 Hz, 2H), 2.84-2.99 (m, 2H) and 3.50 (d, A part of AB, J = 10.2 Hz, 1H), 3.68 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.17 (d and J= 8.4 Hz, 2H) and 7.27 (d and J = 8.4 Hz, 2H), 7.61 (s, 1H), 8.59 (s, 1H), and 9.97.(s, 1H) MS (EI) m/z; 434 [M+1] +361 (bp) . [0084] synthetic example 7 transformer-6-acetylamino -3, 4-dihydro-2, and 2-dimethyl-7-nitro-4- [2-(4-aminophenyl) ethylamino]-2H-1-benzopyran-3-oar [0085]
[Formula 17]

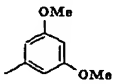
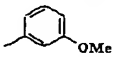
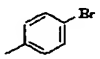


[0086] Yield 40 %1 H-NMR delta (CDCl3):1.17 (s, 3H), 1.48 (s, 3H) and 1.69 (br s, 4H), 2.28 (s, 3H) and 2.71 (t and J = 6.8 Hz, 2H), 2.79-2.92 (m, 2H) and 3.48 (d, A part of AB, J = 10.3 Hz, 1H), 3.67 (dd, B part of AB, J = 10.3 and 1.1 Hz, 1H), 6.63 (d and J = 8.6 Hz, 2H) and 7.02 (d and J = 8.6 Hz, 2H), 7.60 (s, 1H), 8.58 (s, 1H), and 9.96.(s, 1H) MS (EI) m/z; 415[M+1] +237(bp). [0087] synthetic example 8 transformer-6-acetylamino -3, 4-dihydro-2, and 2-dimethyl-7-nitro-4- [2-(4-nitrophenyl) ethylamino]-2H-1-benzopyran-3-oar [0088]
[Formula 18]

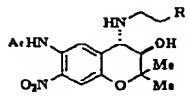


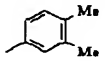
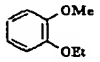
[0089] Yield 19 %mp.: 211-213 **C 1 (decomposition) H-NMR delta (DMSO-d6): 1.15 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 3.05-3.40 (m, 5H), 4.06 (m 1H), 4.51 (m, 1H), and 6.44 (s, 1H), 7.40 (s, 1H) and 7.56 (d and J = 8.8 Hz, 2H), 7.90 (s, 1H), 8.20 (d and J = 8.8 Hz, 2H), and 10.14.(s, 1H) MS (EI) m/z; 444 [M] +371 (bp) . [0090] The synthetic examples 9-36 [0091]
[Formula 19]



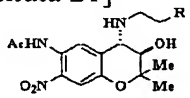
化合物No.	R
合成例9	
合成例10	
合成例11	
合成例12	
合成例13	
合成例14	
合成例15	

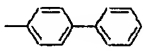
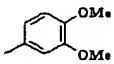
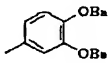
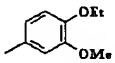
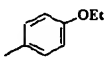
[0092]
[Formula 20]



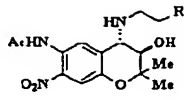
化合物No.	R
合成例16	
合成例17	
合成例18	
合成例19	
合成例20	
合成例21	
合成例22	

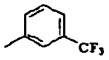
[0093]
[Formula 21]



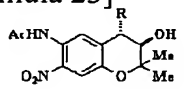
化合物No.	R
合成例23	
合成例24	
合成例25	
合成例26	
合成例27	
合成例28	
合成例29	

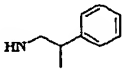
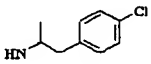
[0094]
[Formula 22]



化合物No.	R
合成例３０	
合成例３１	
合成例３２	
合成例３３	

[0095]
[Formula 23]

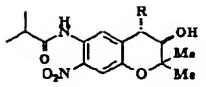


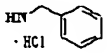
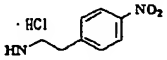
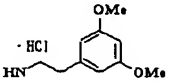
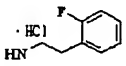
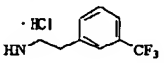
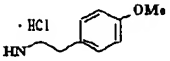
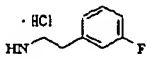
化合物No.	R
合成例３４	
合成例３５	
合成例３６	

[0096] The synthetic example 9 [0097] Red crystal mp. : 176.5-178.0 **C1 H-NMR delta (CDCl3): 1.17 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), and 2.86-2.98 (m, 4H), 3.46 (d and J = 10.0 Hz, 1H) and 3.68 (d and J = 10.0 Hz, 1H), 7.00-7.10 (m, 2H) and 7.17-7.26 (m, 2H), 7.61 (s, 1H), 8.63 (s, 1H), and 9.98.(s, 1H) MS (EI) m / z; 418[M+1]+, 346, 309, and 179 (bp) . [0098] The synthetic example 10 [0099] Red crystal mp. : 163.5-165.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), and 2.81-2.99 (m, 4H), 3.49 (d and J = 10.1 Hz, 1H) and 3.68 (d and J = 10.1 Hz, 1H), 6.89-6.95 (m, 2H) and 7.02 (d and J = 7.6 Hz, 1H), 7.23-7.26 (m, 1H), 7.61 (s, 1H), 8.58 (s, 1H), and 9.96.(s, 1H) MS (EI) m/z; 418 [M+1] +344 and 298 (bp) . [0100] The synthetic example 11 [0101] Orange crystal mp. : 141.0-142.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), and 2.78-2.97 (m, 4H), 3.49 (d and J = 10.1 Hz, 1H) and 3.68 (d and J = 10.1 Hz, 1H), 6.99 (t and J= 8.8 Hz, 2H) and 7.19 (dd, J = 2.9, 5.5 Hz, 2H), 7.61 (s, 1H), 8.57 (s, 1H), and 9.97.(s, 1H) MS (EI) m/z; 417 [M] +345, 302, and 176 (bp) . [0102] The synthetic example 12 [0103] Yellow crystal mp. : 151.0-152.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), and 2.77 (t and J =6.8 Hz, 2H), 2.87-2.97 (m, 2H) and 3.51 (d and J = 10.1 Hz, 1H), 3.69 (d and J =10.1 Hz, 1H) and 6.33 (d and J = 2.2 Hz, 1H), 6.39 (d and J = 2.2 Hz, 2H), 7.60 (s, 1H), 8.55 (s, 1H), and 9.93.(s, 1H) MS (EI) m/z; 459 [M] +441, 307, 278, and 193 (bp) . [0104] The synthetic example 13 [0105] Red amorphous substance 1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), and 2.78-2.97 (m, 4H), 3.50 (d and J = 10.1 Hz, 1H) and 3.69 (d and J = 10.1 Hz, 1H), 3.79 (s, 3H) and 6.75-6.83 (m, 3H), 7.21 (t and J = 7.6 Hz, 1H), 7.60 (s, 1H), 8.56 (s, 1H), 9.94.(s, 1H) MS (FAB) m/z; 430 [M+1] + (bp) . [0106] The synthetic example 14 [0107] Red crystal mp. : 171.5-172.8 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), and 2.86-2.98 (m, 4H), 3.48 (d and J = 10.4 Hz, 1H) and 3.70 (d and J = 10.4 Hz, 1H), 7.14-7.22 (m, 2H) and 7.26-7.28 (m, 1H), 7.34 (dd, J = 1.6, 7.6 Hz, 1H), 7.61 (s, 1H), 8.64 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; +357, 433 [M+1] 318(bp). [0108] The synthetic example 15 [0109] Yellow amorphous substance 1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), and 2.79 (t and J =6.9 Hz, 2H), 2.86-2.98 (m,

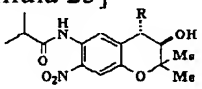
2H) and 3.50 (d and J = 10.1 Hz, 1H), 3.68 (d and J =10.1 Hz, 1H) and 7.12 (d and J = 8.2 Hz, 2H), 7.42 (d and J = 8.2 Hz, 2H), 7.61 (s, 1H), 8.60 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; 481[M+2] +479[M]+ and 406 (bp) . [0110] The synthetic example 16 [0111] Orange crystal mp. : 90.0-91.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.48 (s, 3H), 2.22 (s, 3H), and 2.24 (s, 3H), 2.27 (s, 3H) and 2.75-2.78 (m, 2H), 2.88-2.91 (m, 2H) and 3.50 (d, J = 10.1 Hz, 1H), 3.69 (d and J = 10.1 Hz, 1H) and 6.96 (d and J = 7.7 Hz, 1H), 7.00 (s, 1H) 7.06 (d and J = 7.7 Hz, 1H), 7.60 (s, 1H), 8.61 (s, 1H), and 9.97.(s, 1H) MS (EI) m/z; 428 [M+1] + 356 (bp) . [0112] The synthetic example 17 [0113] Brown amorphous substance 1 H-NMR delta (CDCl3): 1.16 (s, 3H), 1.48 (s, 3H), 2.29 (s, 3H), and 2.82 (brs, 1H), 3.25 (dd, J = 2.1, 7.7 Hz, 2H), 3.52 (d and J = 10.3 Hz, 1H) and 3.69 (d and J = 10.3 Hz, 1H), 7.18-7.35 (m, 10H), 7.61 (s, 1H), 8.61 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; 475 [M+1] +310 and 280 (bp) . [0114] The synthetic example 18 [0115] Yellow crystal mp.186.0-188.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.46 (t and J = 7.1 Hz, 3H) and 1.49 (s, 3H), 2.27 (s, 3H) and 2.78-3.02 (m, 4H), 3.55 (d and J = 10.3 Hz, 1H) and 3.76 (d and J =10.3 Hz, 1H), 4.11 (q and J = 7.1 Hz, 2H) and 6.76-6.82 (m, 3H), 7.61 (s, 1H), 8.53 (s, 1H), and 9.93.(s, 1H) MS (EI) m/z; 473 [M+1] +440, 401, and 308 (bp) . [0116] The synthetic example 19 [0117] Brown amorphous substance 1 H-NMR delta (CDCl3): 1.19 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), and 2.84-2.95 (m, 4H), 3.51 (d and J = 10.4 Hz, 1H) and 3.71 (d and J = 10.4 Hz, 1H), 7.18 (dd, J= 2.0, 8.0 Hz, 1H), 7.22 (d and J = 8.0 Hz, 1H) and 7.36 (d and J = 2.0 Hz, 1H), 7.61 (s, 1H), 8.63 (s, 1H), and 9.99.(s, 1H) MS (EI) m/z; 468 [M] +396 and 353 (bp) . [0118] The synthetic example 20 [0119] Red crystal mp. : 156.0-157.0 **C1 H-NMR delta (CDCl3): 1.19 (s, 3H), 1.50 (s, 3H), 2.28 (s, 3H), and 2.93-3.04 (m, 4H), 3.52 (d and J = 10.1 Hz, 1H) and 3.71 (d and J = 10.1 Hz, 1H), 6.88 (d and J= 3.3 Hz, 1H) and 6.95 (dd, J = 3.3, 5.1 Hz, 1H), 7.16 (d and J = 5.1 Hz, 1H), 7.62 (s, 1H), 8.64 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; 405 [M] +332 and 308 (bp) . [0120] The synthetic example 21 [0121] Brown crystal mp. : 172.0-174.0 **C1 H-NMR delta (CDCl3): 1.19 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), and 2.84 (t and J =6.6 Hz, 2H), 2.90-3.03 (m, 2H) and 3.53 (d and J = 10.1 Hz, 1H), 3.71 (d and J =10.1 Hz, 1H) and 7.18 (d and J = 5.9 Hz, 2H), 7.62 (s, 1H), 8.49 (d, J = 5.9 Hz, 2H), 8.64 (s, 1H), 9.98.(s, 1H) MS (FAB) m/z; 401 [M+1] +171 and 157 (bp) . [0122] The synthetic example 22 [0123] Brown amorphous substance 1 H-NMR delta (CDCl3): 1.20 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), and 2.80-2.87 (m, 3H), 2.93-2.96 (m, 1H) and 3.58 (d and J = 10.3 Hz, 1H), 3.75 (d and J = 10.3 Hz, 1H) and 7.24 (m, 1H), 7.60 (s, 1H) and 7.62 (d and J = 1.5 Hz, 1H), 8.42 (t and J= 1.5 Hz, 2H), 8.67 (s, 1H), and 9.96.(s, 1H) MS (EI) m/z; 400 [M] +328 and 280 (bp) . [0124] The synthetic example 23 [0125] Orange crystal mp. : 147.0-149.0 **C1 H-NMR delta (CDCl3): 1.24 (s, 3H), 1.54 (s, 3H), 2.26 (s, 3H), and 2.94-3.07 (m, 2H), 3.19-3.21 (m, 2H) and 3.66 (d and J = 10.1 Hz, 1H), 3.76 (d and J = 10.1 Hz, 1H) and 7.16-7.19 (m, 1H), 7.22 (d and J = 7.7 Hz, 1H) and 7.58 (s, 1H), 7.63-7.68 (m, 1H), 8.53 (s, 1H), 8.71 (s, 1H), 9.94.(s, 1H) MS (FAB) m/z; 400 [M] +366, 328, and 120 (bp) . [0126] The synthetic example 24 [0127] Brown amorphous substance 1 H-NMR (CDCl3) delta: 1.14 (s, 3H) and 1.45 (s, 3H), 2.24 (s, 3H) and 2.91-3.02 (m, 4H), 3.51 (d and J = 10.3 Hz, 1H) and 3.67 (d and J = 10.3 Hz, 1H), 7.10 (t and J= 7.0 Hz, 1H) and 7.14 (d and J = 2.2 Hz, 1H), 7.20 (J [t and] = 7.0 Hz, 1H) 7.37 (d and J = 8.1 Hz, 1H), 7.57 (d and J = 8.1 Hz, 1H) and 7.59 (s, 1H), 8.10 (brs, 1H), 8.43 (s, 1H), 9.82.(s, 1H) MS (FAB) m/z; 437 [M-1] +307, 278, 233, and 194 (bp) . [0128] The synthetic example 25 [0129] Brown amorphous substance 1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.49 (s, 3H), 2.23 (s, 3H), and 2.87 (t and J =6.8 Hz, 2H), 2.94-2.99 (m, 2H) and 3.52 (d and J = 10.1 Hz, 1H), 3.70 (d and J =10.1 Hz, 1H) and 7.30-7.35 (m, 3H), 7.41-7.45 (m, 2H) and 7.52-7.59 (m, 4H), 7.60 (s, 1H), 8.61 (s, 1H), and 9.96(s, 1H).MS (EI) m/z; 475 [M] +442 and 401 (bp) . [0130] The synthetic example 26 [0131] Red amorphous substance 1 H-NMR delta (CDCl3): 1.19 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), and 2.76-2.79 (m, 2H), 2.84-2.90 (m, 1H) and 2.93-2.98 (m, 1H), 3.53 (d and J = 10.1 Hz, 1H) and 3.70 (d and J = 10.1 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), and 6.76-6.81 (m, 3H), 7.60 (s, 1H), 8.54 (s, 1H), and 9.93.(s, 1H) MS (EI) m/z; 460 [M+1] +237 and 165 (bp) . [0132] The synthetic example 27 [0133] 58 % Yield Yellow Crystal Mp.225 **C1 H-NMR Delta (DMSO-d6): 1.15 (S, 3H), 1.45 (s, 3H), 2.04 (s, 3H), 2.90-3.10 (m, 5H), 3.21 (br s, 1H) and 4.00-4.05 (m, 1H), 4.47-4.51 (m, 1H) and 5.09 (s, 2H), 5.12 (s, 2H) and 6.75 (dd, J = 8.2 and 1.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H) and 7.03 (d and J = 2.0 Hz, 1H), 7.28-7.46 (m, 11H), 7.96 (s, 1H), and 10.20.(s, 1H) MS (EI) m/z; 611 [M] + (bp) . [0134] The synthetic example 28 [0135] 32 % Yield Yellow Crystal Mp.227-228 **C1 H-NMR Delta (DMSO-d6) : 1.15 (S, 3H), 1.29 (t and J = 7.0 Hz, 3H) and 1.45 (s,

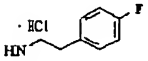
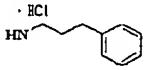
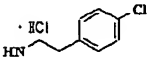
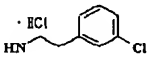
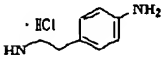
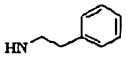
3H), 2.05 (s, 3H) and 2.90-3.10 (m, 4H), 3.25 (br s, 1H) and 3.74 (s, 3H), 3.96 (q and J = 7.0 Hz, 2H) and 4.00-4.05 (br s, 1H), 4.42 (br s, 1H) and 6.45 (br s, 1H), 6.73 (dd, J = 8.4 and 2.4 Hz, 1H), 6.85 (d and J = 2.4 Hz, 1H) and 6.86 (d and J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.92 (s, 1H), and 10.16.(s, 1H) MS (EI) m/z; 473 [M] +233 (bp) . [0136] The synthetic example 29 [0137] 40 % Yield Yellow Amorphous Substance 1 H-NMR Delta (CDCl3): 1.11 (S, 3H), 1.30 (t and J = 7.0 Hz, 3H) and 1.91 (s, 3H), 2.00 (s, 3H) and 2.45-2.50 (m, 2H), 2.65 (t and J = 7.1 Hz, 2H) and 2.75-2.85 (m, 1H), 3.58 (dd, A part of AB, J = 9.6 and 5.3 Hz, 1H), 3.65 (d, B part of AB, J = 9.6 Hz, 1H), 3.97 (q and J = 7.0 Hz, 2H) and 5.43 (d and J = 5.3 Hz, 1H), 6.80 (d and J = 8.8 Hz, 2H) and 7.10 (d and J = 8.8 Hz, 2H), 7.60 (s, 1H), 8.32 (s, 1H), and 9.95.(s, 1H) MS (EI) m / z;443 [M] +237 (bp) . [0138] The synthetic example 30 [0139] 98 % Yield Yellow Crystal Mp.214-216 **CMS (EI) M/Z; 467 [M] +308 (Bp) . [0140] The synthetic example 31 [0141] 96 % Yield Orange Crystal Mp.133-134 **C1 H-NMR (CDCl3) delta: 1.18 (s, 3H) and 1.49 (s, 3H), 1.60 (br s, 1H), 2.28 (s, 3H), and 2.75-3.00 (m, 5H), 3.50 (d, A part of AB, J = 10.2 Hz, 1H), 3.69 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.05-7.20 (m, 4H), 7.61 (s, 1H), 8.59 (s, 1H), and 9.97.(s, 1H) MS (EI) m/z; 433 [M] + (bp) . [0142] The synthetic example 32 [0143] 82 % Yield Orange Solid 1 H-NMR Delta (CDCl3): 1.18 (S, 3H), 1.48 (s, 3H), 2.27 (s, 3H), and 2.80-3.00 (m, 6H), 3.49 (d, A part of AB, J = 10.1 Hz, 1H), 3.69 (dd, B part of AB, J = 10.1 and 1.2 Hz, 1H), 7.40-7.50 (m, 4H), 7.62 (s, 1H), 8.63 (s, 1H), and 9.99.(s, 1H) MS (EI) m/z; 467 [M] +348 (bp) . [0144] The synthetic example 33 [0145] 84 % Yield Yellow Amorphous Substance 1 H-NMR Delta (CDCl3): 1.19 (S, 3H), 1.49 (s, 3H) and 1.58 (br s, 1H), 2.27 (s, 3H) and 2.80-2.98 (m, 3H), 3.08-3.23 (m, 2H) and 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.72 (d, B part of AB, J = 10.3 Hz, 1H), 7.02-7.08 (m, 1H), 7.25-7.28 (m, 2H), 7.61 (s, 1H), 8.68 (s, 1H), and 10.00.(s, 1H) MS (EI) m/z; 467 [M] +354 (bp) . [0146] The synthetic example 34 [0147] Yellow crystal mp. : 160.0-165.0 **C1 H-NMR delta (CDCl3): 1.33 (s, 3H), 1.53 (s, 3H), 2.14 (s, 3H), and 2.61 (d and J =2.8 Hz, 1H), 3.79 (dd, J = 2.8, 8.8 Hz, 1H), 3.99 (d and J = 8.8 Hz, 1H) and 6.78 (d and J = 8.0 Hz, 2H), 6.83 (t and J = 7.6 Hz, 1H) and 7.23 (t, J = 8.0 Hz, 2H), 7.66 (s, 1H), 8.59 (s, 1H), and 9.79.(s, 1H) MS (EI) m/z; 371 [M] +299 and 257 (bp) . [0148] The synthetic example 35 [0149] 87 % Yield Yellow Amorphous Substance, Diastereomer 1:1 Mixture
1 H-NMR delta (CDCl3): 1.15 (s, 6H) and 1.29 (d and J = 5.5 Hz, 6H), 1.45 (s, 3H), 1.48 (s and 3 H), and 2.28 (s, 3H), 2.29 (s, 3H) and 2.58 (br s, 1H), 2.75-2.90 (m, 8H) and 2.95 (br s, 1H), 3.37 (d and J = 10.0 Hz, 1H) and 3.50 (d, J = 10.0 Hz, 1H), 3.62 (d and J = 10.1 Hz, 1H) and 3.64 (d and J = 10.1 Hz, 1H), 7.20-7.38 (m, 10H) and 7.59 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H), 8.65 (s, 1H), 9.95 (s, 1H), and 10.00.(s, 1H) MS (EI) m/z; 414 [M+1] +279 (bp) . [0150] The synthetic example 36 [0151] 27 % Yield Orange Solid, Diastereomer A(More Polar).1 H-NMR Delta (CDCl3): 1.20 (S, 3H), 1.29 (d and J = 6.5 Hz, 3H) and 1.44 (s, 3H), 1.72 (br s, 2H), 2.26 (s, 3H), and 2.61 (dd, A part of AB, J = 13.4 and 7.1Hz, 1H), 2.86 (dd, B part of AB, J = 13.4 and 6.5 Hz, 1H), 3.28-3.36 (m, 1H) and 3.34 (d, A part of AB, J = 9.7 Hz, 1H), 3.63 (dd, B part of AB, J= 9.7 and 1.1 Hz, 1H), 7.14 (d and J = 8.2 Hz, 2H) and 7.26 (d and J = 8.2 Hz, 2H), 7.60 (s, 1H), 8.84 (s, 1H), and 10.06.(s, 1H) MS (EI) m/z; 447 [M] + (bp) . [0152] 32 % Yield Yellow Solid, Diastereomer B (Less Polar)
1 H-NMR delta (CDCl3): 1.14 (d and J = 6.0 Hz, 3H), 1.23 (s, 3H), 1.49 (s, 3H), and 1.60 (br s, 2H), 2.29 (s, 3H) and 2.76 (d and J = 6.8 Hz, 2H), 3.52 (d, A partof AB, J = 10.0 Hz, 1H), 3.51 (dq, J = 6.8 and 6.0 Hz, 1H), 3.65 (dd, Bpart of AB, J = 10.0 and 1.0 Hz, 1H), 7.25 (s, 4H), 7.56 (s, 1H), 8.54 (s, 1H), and 9.91.(s, 1H) MS (EI) m/z; 447 [M] + (bp) . [0153] The synthetic examples 37-49 [0154] [Formula 24]



化合物No.	R
合成例37	
合成例38	
合成例39	
合成例40	
合成例41	
合成例42	
合成例43	

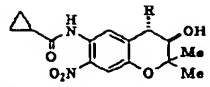
[0155]
[Formula 25]

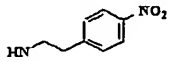
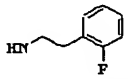
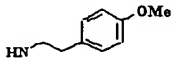
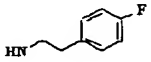
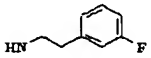
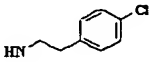


化合物No.	R
合成例44	
合成例45	
合成例46	
合成例47	
合成例48	
合成例49	

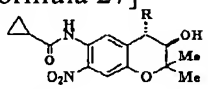
[0156] The general synthesis method in the synthetic examples 37-49 [0157] 6-isopropyl amide -3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (200 mg, 0.65 mmol) Lithium bromide (226mg, 2.6 mmol) Tetrahydrofuran solution (2 mL) An amine (1.31 mmol) is added at a room temperature, and it is at 65 **. 4 Time amount churning was carried out. Ethyl acetate was added, saturation brine washed the organic phase twice, and it dried with sulfuric anhydride magnesium. After distilling off a solvent, the silica gel column chromatography refined residue and the specified substance was obtained as a rough object. Then, methanol solution of the specified substance (10 the amount of double) The bottom of ice-cooling, 10 % hydrogen chloride-methanol solution (2 the amount of double) It adds. 30 It agitated between parts. Diisopropyl ether (100 the amount of double) In addition, separation and diisopropyl ether washed the obtained crystal, and the hydrochloride of the specified substance was obtained. 1 H-NMR was measured for the obtained hydrochloride after the extract in ethyl acetate and a saturation sodium-hydrogencarbonate water

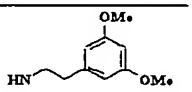
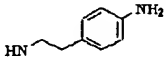
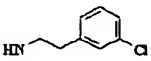
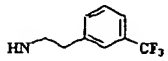
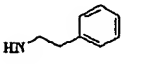
solution.
[0158] The synthetic example 37 [0159] 33 % Yield Yellow Crystal Mp. : 228 **C.(Decomp) MS (FAB) M/Z; 414 [M+H] +. [0160] The synthetic example 38 [0161] 30 % Yield Yellow Crystal Mp. : 257 **C.(Decomp) 1 H-NMR Delta (CDCl3): 1.18 (S, 3H), 1.32 (d and J = 6.8 Hz, 6 H) and 1.49 (s, 3H), 1.60 (br s, 1H) and 2.65 (quint, J = 6.8 Hz, 1H), 2.80 (br s, 1H) and 2.95-3.05 (m, 4H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part ofAB, J = 10.3 Hz, 1H), 7.44 (d and J = 8.4 Hz, 2H) and 7.64 (s, 1H), 8.17 (d and J= 8.4 Hz, 2H), 8.74 (s, 1H), 10.18.(s, 1H) MS (FAB) m/z; 473 [M+H] +. [0162] The synthetic example 39 [0163] 33 % Yield Yellow Crystal Mp. : 244-245 **C. (Decomp) 1 H-NMR Delta (CDCl3): 1.18 (S, 3H), 1.30 (d and J = 6.8 Hz, 6H) and 1.48 (s, 3H), 1.60 (br s, 1H) and 2.63 (quint, J = 6.8 Hz, 1H), 2.77 (t and J = 6.8 Hz, 2H) and 2.95-3.00 (m, 3H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part of AB, J = 10.3 Hz, 1H), 3.78 (s, 6H) and 6.32 (d and J = 2.4 Hz, 1H), 6.40 (d and J = 2.4 Hz, 2H), 7.62 (s, 1H), 8.71 (s, 1H), 10.14.(s, 1H) MS (FAB) m/z; 488 [M+H] +. [0164] The synthetic example 40 [0165] 46 % Yield Yellow Crystal Mp. : 239 **C.(Decomp) MS (FAB) M/Z; 446 [M+H] +. [0166] The synthetic example 41 [0167] 38 % Yield Yellow Crystal Mp. : 249 **C.(Decomp) MS (FAB) M/Z; 496 [M+H] +. [0168] The synthetic example 42 [0169] 23 % Yield Yellow Crystal Mp. : 228 **C.(Decomp) MS (FAB) M/Z; 458 [M+H] +. [0170] The synthetic example 43 [0171] 31 % Yield Yellow Crystal Mp. : 243 **C. (Decomp) MS (FAB) M/Z; 446 [M+H] +. [0172] The synthetic example 44 [0173] 26 % Yield Yellow Crystal Mp. : 242 **C.(Decomp) 1 H-NMR Delta (CDCl3): 1.17 (S, 3H), 1.31 (d and J = 6.9 Hz, 6H) and 1.48 (s, 3H), 2.00 (br s, 2H) and 2.64 (quint, J = 6.9 Hz, 1H), 2.75-3.00 (m, 4H) and 3.50 (d, A part of AB, J = 10.0 Hz, 1H), 3.69 (d, B part of AB, J = 10.0 Hz, 1H), 7.01 (t and J = 8.5 Hz, 2H), 7.15-7.26 (m, 2H), 7.63 (s, 1H), 8.69 (s, 1H), 10.15.(s, 1H) MS (FAB) m/z; 446 [M+H] +. [0174] The synthetic example 45 [0175] 9 % Yield Yellow Crystal Mp. : 112-116 **C.(Decomp) MS (FAB) M/Z; 442 [M+H] +. [0176] The synthetic example 46 [0177] 24 % Yield Yellow Crystal Mp. : 250 **C.(Decomp) 1 H-NMR Delta (CDCl3): 1.18 (S, 3H), 1.32 (d and J = 7.0 Hz, 6H) and 1.49 (s, 3H), 1.62 (br s, 2H) and 2.65 (quint, J = 7.0 Hz, 1H), 2.81 (t and J = 6.6 Hz, 2H) and 2.88-3.00 (m, 2H), 3.48 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, Bpartof AB, J = 10.3 Hz, 1H), 7.18 (d and J = 8.3 Hz, 2H) and 7.26 (d, J = 8.3Hz, 2H), 7.63 (s, 1H), 8.71 (s, 1H), 10.16.(s, 1H) MS (FAB) m/z; 462 [M+H] +. [0178] The synthetic example 47 [0179] 35 % Yield Yellow Crystal Mp. : 249 **C.(Decomp) MS (FAB) M/Z; 462 [M+H] +. [0180] The synthetic example 48 [0181] 16 % Yield Yellow Crystal Mp. : 204-208 **C.(Decomp) MS (FAB) M/Z; 443 [M+H] +. [0182] The synthetic example 49 [0183] Red amorphous substance 1 H-NMR (CDCl3) delta: 1.17 (s, 3H) and 1.32 (d and J = 7.0 Hz, 6H), 1.48 (s, 3H), 2.27 (s, 3H), and 2.65 (q and J = 7.0 Hz, 1H), 2.86-2.98 (m, 4H) and 3.46 (d and J =10.0 Hz, 1H), 3.68 (d and J = 10.0 Hz, 1H) and 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.63 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; 420 [M+1] +344 and 179 (bp) . [0184] The synthetic examples 50-75 [0185]
[Formula 26]



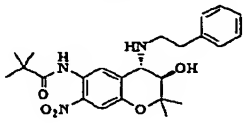
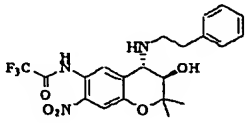
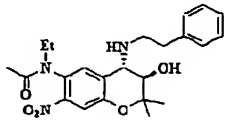
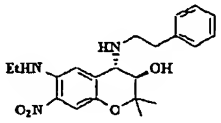
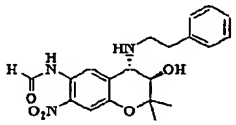
化合物No.	R
合成例５０	
合成例５１	
合成例５２	
合成例５３	
合成例５４	
合成例５５	
合成例５６	

[0186]
[Formula 27]

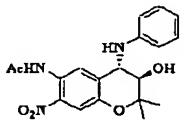
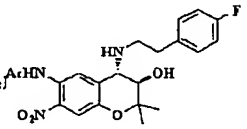
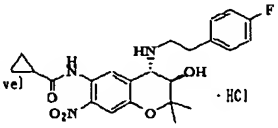
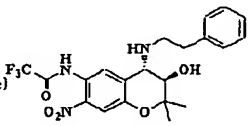


化合物No.	R
合成例５７	
合成例５８	
合成例５９	
合成例６０	
合成例６１	
合成例６２	

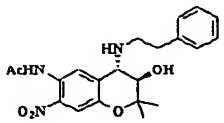
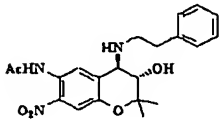
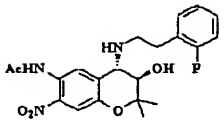
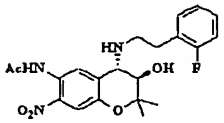
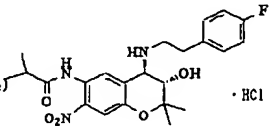
[0187]
[Formula 28]

化合物No.	構造式
合成例6 3	
合成例6 4	
合成例6 5	
合成例6 6	
合成例6 7	

[0188]
[Formula 29]

化合物No.	構造式
合成例6 8 (optically active)	
合成例6 9 (optically active)	
合成例7 0 (optically active)	
合成例7 1 (optically active)	

[0189]
[Formula 30]

化合物No.	構造式
合成例72 (optically active)	
合成例73 (optically active)	
合成例74 (optically active)	
合成例75 (optically active)	
合成例76 (optically active)	

[0190] The general synthesis method in the synthetic examples 50-75 [0191] 6-cyclo propyl amide - 3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (200 mg, 0.66 mmol) Lithium bromide (226mg, 2.6 mmol) Tetrahydrofuran solution (2 mL) At a room temperature, it is an amine (1.31 mmol). It is at 65 ** moreover. 4 Time amount churning was carried out. Ethyl acetate was added, saturation brine washed the organic layer twice, and it dried with sulfuric anhydride magnesium. After distilling off a solvent, the silica gel column chromatography refined residue and the specified substance was obtained.
[0192] The synthetic example 50 [0193] Yield 30%H-NMR [1] delta (CDCl3): 0.96-0.98 (m, 2H), 1.10-1.78 (m, 5H) and 1.48 (s, 3H), 1.63-1.66 (m, 1H) and 2.93-3.01 (m, 4H), 3.52 (d and J =10.1 Hz, 1H) and 6.68 (d and J=10.1 Hz, 1H), 7.40-7.42 (m, 2H) and 7.63 (s, 1H), 8.14-8.17 (m, 2H), 8.66 (s, 1H), and 10.29.(bs, 1H) MS (EI) m/z; 334 (bp) and 471 [M] +. [0194] The synthetic example 51 [0195] Yield 38%H-NMR [1] delta (CDCl3): 0.92-0.95 (m, 2H), 1.09-1.13 (m, 2H) and 1.19 (s, 3H), 1.50 (s, 3H) and 1.63-1.64 (m, 1H), 1.80-1.84 (m, 2H) and 2.58-2.68 (m, 4H), 3.56 (d and J =10.1 Hz, 1H) and 3.71 (dd, J = 0.9, 10.1 Hz, 1H), 7.14-7.27 (m, 5H), 7.61 (s, 1H), 8.72 (d and J =0.9 Hz, 1H), and 10.30.(bs, 1H) MS (EI) m/z; 300 (bp) and 439 [M] +. [0196] The synthetic example 52 [0197] Yield 71%H-NMR [1] delta (CDCl3): 0.94-0.96 (m, 2H), 1.10-1.17 (m, 5H) and 1.47 (s, 3H), 1.63-1.66 (m, 1H) and 2.81-2.94 (m, 4H), 3.50 (d and J =10.1 Hz, 1H) and 3.70 (d and J=10.1 Hz, 1H), 6.96-7.22 (m, 4H), 7.60 (s, 1H), 8.64 (s, 1H), and 10.25.(bs, 1H) MS (EI) m/z; 303 (bp) and 443 [M] +. [0198] The synthetic example 53 [0199] Yield 47%H-NMR [1] delta (CDCl3): 0.93-0.96 (m, 2H), 1.10-1.17 (m, 5H) and 1.48 (s, 3H), 1.63-1.65 (m, 1H) and 2.72-2.89 (m, 4H), 3.50 (d and J =10.1 Hz, 1H) and 3.67 (dd, J = 0.7, 10.1 Hz, 1H), 3.77 (s, 3H) and 6.80-6.82 (m, 2H), 7.10-7.13 (m, 2H), 7.60 (s, 1H), 8.63 (s, 1H), 10.25.(bs, 1H) MS (FAB) m/z; 121 456 [M+1] +. [0200] The synthetic example 54 [0201] Yield 54%H-NMR [1] delta (CDCl3): 0.95-0.97 (m, 2H), 1.10-1.17 (m, 2H) and 1.26 (s, 3H), 1.48 (s, 3H) and 1.63-1.67 (m, 1H), 2.76-2.94 (m, 4H) and 3.50 (d and J =10.2 Hz, 1H), 3.67 (dd, J = 1.0, 10.2 Hz, 1H), 6.94-6.99 (m, 2H) and 7.15-7.26 (m, 2H), 7.61 (s, 1H), 8.61 (d and J =1.0 Hz, 1H), and 10.26.(bs, 1H) MS (EI) m/z; 260 (bp) and 443 [M] +. [0202] The synthetic example 55 [0203] Yield 53%H-NMR [1] delta (CDCl3): 0.94-0.97 (m, 2H), 1.11-1.17 (m, 5H) and 1.48 (s, 3H), 1.63-1.65 (m, 1H) and 2.79-2.94 (m, 4H), 3.49 (d and J =10.3 Hz, 1H) and 3.67 (dd, J = 0.9, 10.3 Hz, 1H), 6.90-7.01 (m, 3H) and 7.23-7.26 (m, 1H), 7.62 (s, 1H), 8.63 (d and J =0.9 Hz, 1H), and 10.27.(bs, 1H) MS (EI) m/z; 301 (bp), 443[M]+. [0204] The synthetic example 56 [0205] Yield 58%H-NMR [1] delta (CDCl3): 0.87-0.90 (m, 2H), 1.11-1.14 (m, 2H) and 1.17 (s, 3H), 1.48 (s, 3H) and 1.63-1.67 (m, 1H), 2.77-2.81 (m, 2H) and 2.89-2.93 (m,

2H), 3.48 (d and J =10.3 Hz, 1H) and 3.65 (d and J =10.3 Hz, 1H), 7.16-7.26 (m, 4H), 7.62 (s, 1H), 8.65 (s, 1H), and 10.28.(bs, 1H) MS (EI) m/z; 305 (bp) and 460 [M] +. [0206] The synthetic example 57 [0207] Yield 56%H-NMR [1] delta (CDCl3): 0.92-0.95 (m, 2H), 1.09-1.18 (m, 5H) and 1.49 (s, 3H), 1.62-1.65 (m, 1H) and 2.73-2.92 (m, 4H), 3.51 (d, J = 10.2Hz, 1H) and 3.67 (d and J=10.2 Hz, 1H), 3.77 (s, 6H), 6.31 (s, 3H), and 6.37 (s, 2H), 7.61 (s, 1H), 8.64 (s, 1H), and 10.26.(bs, 1H) MS (EI) m/z; 470 (bp) and 486 [M] +. [0208] The synthetic example 58 [0209] Yield 52%1 H-NMR (CDCl3) delta: 0.92-0.97 (m, 2H) and 1.10-1.16 (m, 2H), 1.20 (s, 3H), 1.51 (s, 3H), and 1.63-1.68 (m, 1H), 3.64 (d and J =10.1 Hz, 1H) and 3.77-3.84 (m, 3H), 7.25-7.39 (m, 5H), 7.67 (s, 1H), 8.88 (s, 1H), and 10.34.(bs, 1H) MS (EI) m/z; 339 (bp) and 411 [M] +. [0210] The synthetic example 59 [0211] Yield 57%H-NMR [1] delta (CDCl3): 0.93-0.96 (m, 2H), 1.11-1.17 (m, 5H) and 1.47 (s, 3H), 1.63-1.65 (m, 1H) and 2.68-2.71 (m, 2H), 2.85-2.88 (m, 2H) and 3.46 (d, J = 10.1Hz, 1H), 3.64 (d and J =10.1 Hz, 1H) and 6.62-6.64 (m, 2H), 6.70-7.02 (m, 2H), 7.61 (s, 1H), 8.64 (s, 1H), and 10.26.(bs, 1H) MS (EI) m/z; 333 (bp) and 439 [M] +. [0212] The synthetic example 60 [0213] Yield 42%H-NMR [1] delta (CDCl3): 0.94-0.97 (m, 2H), 1.12-1.17 (m, 5H) and 1.49 (s, 3H), 1.63-1.67 (m, 1H) and 2.77-2.94 (m, 4H), 3.49 (d and J =10.3 Hz, 1H) and 3.67 (dd, J = 0.9, 10.3 Hz, 1H), 7.10-7.22 (m, 4H), 7.62 (s, 1H), 8.63 (d and J =0.9 Hz, 1H), and 10.27.(bs, 1H) MS (EI) m/z; 334 (bp) and 460 [M] +. [0214] The synthetic example 61 [0215] Yield 61%H-NMR [1] delta (CDCl3): 0.94-0.97 (m, 2H), 1.10-1.18 (m, 5H) and 1.48 (s, 3H), 1.63-1.66 (m, 1H) and 2.85-2.96 (m, 4H), 3.53 (d and J =10.1 Hz, 1H) and 3.71 (d and J=10.1 Hz, 1H), 7.28-7.46 (m, 4H), 7.60 (s, 1H), 8.66 (s, 1H), and 10.26.(bs, 1H) MS (EI) m/z; 259 (bp) and 494 [M] +. [0216] The synthetic example 62 [0217] Red amorphous substance 1 H-NMR delta (CDCl3): 0.94-0.97 (m, 2H), 1.12-1.15 (m, 2H) and 1.16 (s, 3H), 1.47 (s, 3H) and 1.61-1.67 (m, 1H), 2.79-2.96 (m, 4H) and 3.45 (d and J = 9.9 Hz, 1H), 3.64 (d and J = 9.9 Hz, 1H) and 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.62 (s, 1H), and 10.26 MS (s, 1H) (EI) m/z; 418 [M+1] +346, 309, and 179 (bp) . [0218] The synthetic example 63 [0219] Red crystal mp. : 169.0-170.0 **C1 H-NMR delta (CDCl3): 1.17 (s, 3H), 1.37 (s, 9H), 1.47 (s, 3H), and 2.81-2.85 (m, 2H), 2.93-2.97 (m, 2H) and 3.47 (d and J = 10.1 Hz, 1H), 3.67 (d and J = 10.1 Hz, 1H) and 7.19-7.32 (m, 5H), 7.63 (s, 1H), 8.74 (s, 1H), and 10.44.(s, 1H) MS (EI) m/z; 441 [M+1] +322 and 268 (bp) . [0220] The synthetic example 64 [0221] Red crystal mp. : 176.5-178.0 **C1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.54 (s, 3H) and 3.05-3.16 (m, 3H), 3.26-3.30 (m, 1H) and 4.06 (d and J = 8.6 Hz, 1H), 4.58 (d and J = 8.6 Hz, 1H) and 7.15-7.26 (m, 5H), 7.73 (s, 1H), 8.65 (s, 1H), and 10.66.(s, 1H) MS (EI) m/z; 453 [M] + (bp) . [0222] The synthetic example 65 [0223] Red amorphous substance 1 H-NMR delta (CDCl3): 1.02 (t and J = 6.8 Hz, 3H), 1.24 (s, 3H), 1.52 (s, 3H), and 1.83 (s, 3H), 2.68-2.96 (m, 4H) and 3.33 (q and J = 6.8 Hz, 1H), 3.63 (d and J =10.1 Hz, 1H) and 3.74 (d and J = 10.1 Hz, 1H), 3.77-3.90 (m, 1H), 7.19-7.39.(m, 7H) MS (FAB) m/z; 428 [M] + (bp), 268, 105. [0224] The synthetic example 66 [0225] Red amorphous substance 1 H-NMR (CDCl3) delta: 1.15 (s, 3H) and 1.33 (t and J = 7.1 Hz, 3H), 1.46 (s, 3H) and 2.82-2.86 (m, 3H), 2.91-2.96 (m, 1H) and 3.08-3.13 (m, 2H), 3.59 (d and J = 10.1 Hz, 1H) and 3.65 (d and J = 10.1 Hz, 1H), 6.58 (s, 1H) and 7.22-7.26 (m, 3H), 7.31-7.34 (m, 2H), 7.53 (brs, 1H), 7.60 (s, 1H), and MS (EI) m/z; 385 [M] +314, 266, and 223 (bp) . [0226] The synthetic example 67 [0227] Yellow oily matter 1 H-NMR delta (CDCl3): 1.18 (s, 3H), 1.48 (s, 3H) and 2.75-3.00 (m, 6H), 3.52 (d, A part of AB, J = 9.9 Hz, 1H), 3.70 (d, B part of AB, J = 9.9 Hz, 1H), 7.18-7.35 (m, 5H), 7.62 (s, 1H), 8.45 (s, 1H), 8.66 (s, 1H), and 9.98.(s, 1H) MS (EI) m/z; 385[M] +313(bp). [0228] The synthetic example 68 [0229] (+) -(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to induction yellow amorphous substance [alpha] [26D+104.6 [(c 0.64, EtOH)0230]] The synthetic example 69 [0231] (+) -(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two - From dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to an induction yellow crystal (HCl salt) : [mp.] 246-247 **C. (decomp) (HCl salt) : [alpha] D26-71.8 [(c 0.38, EtOH) 0232] The synthetic example 70 [0233] (+) -(3R*, 4R*)-3, the 4-epoxy-6-cyclo propyl amide -3, 4-dihydro - 2 Two - From dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to an induction (HCl salt):yellow crystal () [HCl] [ ] salt: mp.241-246 **C. (decomp) (HCl salt) : [alpha] 26D-92.1 [(c 0.45, EtOH)0234] The synthetic example 71 [0235] (+) -(3R*, 4R*)-3, 4-epoxy -3, 4-dihydro - 2 and 2-dimethyl -7 - From nitro-6-trifluoroacetamide-2H-1-benzopyran (99% ee above) to an induction (HCl salt):yellow crystal () [HCl] [ ] salt: mp.243 **C. (decomp) [alpha] 26D-54.8 [(c 0.5, EtOH) 0236] Synthetic example 72(+)-(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two -

Dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to induction red amorphous substance [alpha] 26D-64.3 [(c 1.03, EtOH)0237] The synthetic example 73 [0238] (-) -(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to induction red amorphous substance [alpha] [26D+61.2 [(c 0.98, EtOH)0239]] The synthetic example 74 [0240] (+) -(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to induction red amorphous substance [alpha] [26D-64.6 [(c 1.00, EtOH)0241]] The synthetic example 75 [0242] (-) -(3R*, 4R*)-6-acetamido -3, 4-epoxy -3, 4-dihydro - 2 Two - Dimethyl-7-nitro-2H-1-benzopyran (99% ee above) to induction red amorphous substance [alpha] [26D+60.8 [(c 0.93, EtOH)0243]] synthetic example 76 (+) - (3R*, 4R*) -3, the 4-epoxy-6-isopropyl amide -3, 4-dihydro-2, and 2-dimethyl-7-nitro-2H-1-benzopyran (1.0 g, 3.59 mmol) Lithium bromide (1.24 g, 14.36 mmol) Acetonitrile solution (10 mL) At a room temperature 4-fluoro phenethylamine which is equivalent to a substituent the 4th place, respectively (1.88 mL, 14.4 mmol) It adds. With 65 ** 2 Time amount churning was carried out. Ethyl acetate was added, a saturation sodium-hydrogencarbonate solution and saturation brine washed the organic phase, and it dried with sulfuric anhydride magnesium. After distilling off a solvent, the silica gel column chromatography refined residue and the 4th place of an amine substitution product was obtained. Then, ethanol solution of 4 place amine substitution product (10 the amount of double) It is concentrated hydrochloric acid at a room temperature. (6 equivalent) It adds. 90 **C 1 Japan-Canada heat reflux was carried out. A saturation sodium-hydrogencarbonate solution is added and they are an extract and an organic phase with saturation brine at ethyl acetate 1 Time washing was carried out and it dried with sulfuric anhydride magnesium. A solvent is distilled off and the 4th place of 6 place deamidation object of an amine substitution product is gained. **. Then, dimethylformamide solution of 6 place deamidation object (20 the amount of double) At a room temperature 4 Convention hydrogen chloride-dioxane solution (1.4 equivalent) It is 10 moreover. It agitated between parts. Acid chloride corresponding to a substituent the 6th place (1.5 equivalent) It is dropped. 1 It time-amount-agitates, continues and is a methanol (1 mL). It is a pan moreover. 10 It agitated between parts. Water was added, ethyl acetate washed the extract and the organic phase with a saturation sodium-hydrogencarbonate solution and saturation brine, and it dried with sulfuric anhydride magnesium. After distilling off a solvent, the silica gel column chromatography refined residue and the specified substance was obtained. Then, methanol solution of the specified substance (10 the amount of double) The bottom of ice-cooling, 10 % hydrogen chloride-methanol solution (2 the amount of double) It adds. 30 It agitated between parts. Diisopropyl ether (100 the amount of double) In addition, separation and diisopropyl ether washed the obtained crystal, and the hydrochloride of the specified substance was obtained.

[0244] Yellow crystal mp. : 244-245 **C. (decomp) [alpha] 26D-67.3 [(c 0.4, EtOH)0245] [The example of pharmaceutical preparation]

[0246] An example of pharmaceutical preparation 1 tablet this invention compound 10g milk Sugar 260g microcrystal cellulose 600g corn starch 350g hydroxypropylcellulose 100 gCMC-calcium 150g magnesium stearate 30g ** Amount After mixing the 1,500g above-mentioned component with a conventional method, sugar-coated tablet 10,000 lock which contains a 1mg active ingredient in 1 lock is manufactured.

[0247] Example of pharmaceutical preparation 2 capsule this invention compound 10g milk Sugar 440g microcrystal cellulose 1,000g magnesium stearate 50g ** Amount After mixing the 1,500g above-mentioned component with a conventional method, a gelatine capsule is filled up, and capsule 10,000 capsule which contains a 1mg active ingredient in 1 capsule is manufactured.

[0248] An example of pharmaceutical preparation 3 elastic-capsule this invention compound 10gPEG(s)400 479g saturated fatty acid triglyceride 1,500g mentha oil The 1g polysorbate 80 (Polysorbate) 10g ** Amount After mixing the 2,000g above-mentioned component, a No. 3 ** gelatine capsule is filled up with a conventional method, and elastic capsule 10,000 capsule which contains a 1mg active ingredient in 1 capsule is manufactured.

[0249] Example of pharmaceutical preparation 4 ointment this invention compound 1.0g liquid paraffin 10.0g cetanol 20.0g white vaseline 68.4g ethylparaben 0.1gl-menthol 0.5g ** Amount The 100.0g above-mentioned component is mixed with a conventional method, and it considers as ointment 1%.

[0250] Example of pharmaceutical preparation 5 suppositories this invention compound 1gWITTEPPUZORUH15* 478gWITTEPPUZORUW35* 520g BORISORU bait 80 (Polysorbate) 1g ** Amount 1,000g "brand-name WITTEPPUZORU =Witepsol of * triglyceride system compound"
1,000 1g suppositories which carry out melting mixing of the above-mentioned component with a conventional method, flow into a suppositories container, carry out cooling solidification, and contain a 1mg active ingredient are manufactured.
[0251] Example of pharmaceutical preparation 6 injections this invention compound 1mg distilled water for injection It dissolves and uses at the time of the object for 5mL.
[0252] [Example of a pharmacological test] The heart was extracted and the left artium or papillary muscles of right ventricle was separated from the effect test-method guinea pig exerted on the refractory period in a left-artium muscle and papillary muscles of right ventricle in the Krebs-Henseleit solution which carried out aeration of CO2 95%O2+5%. The sample was stimulated using electrostimulator with the threshold 1.5 times the electrical potential difference of reacted to 1Hz and a stimulus (a fundamental stimulus; S1), and recorded the contraction then generated on the thermal stylus recorder through FD pickup and distorted pressure amplifier. The refractory period was defined as smallest spacing between S1 which measurable contraction produces as a result, and a special stimulus (S2). spacing of S1 and S2 -- a left-artium muscle sample -- from 150 m seconds -- starting -- 100 m seconds ****** -- 10 -- every m seconds and after that -- 5 -- it is shortened until it continues till a refractory period by a unit of m second -- making -- a papillary-muscles-of-right-ventricle sample -- from 300 m seconds -- starting -- 10 -- you made it shortened until it continued till a refractory period by a unit of m second In addition, S2 was set up the twice of a threshold reacted to a stimulus. Experiment temperature was made into 36**1 degree C. in addition, a solvent -- a left-artium muscle and papillary muscles of right ventricle -- it influenced at neither of the refractory periods. After measuring the fundamental value before adding a compound, the refractory period was measured, after adding cumulatively and carrying out the incubation of the compound for each concentration 15 minutes.
[0253] The compound concerning result this invention showed the powerful refractory period extension operation to the atrium.
[0254]
[Table 1]

化合物 (合成例No.)	不応期延長 EC_{20} (μM)	化合物 (合成例No.)	不応期延長 EC_{20} (μM)
1	6.1	5	5.5
3	4.0	6	1.4
4	5.0	8	1.8

[0255]
[Effect of the Invention] this invention compound shows a refractory period extension operation, and is useful to the improvement of arrhythmia. Therefore, this invention can offer a useful antiarrhythmic.

[Translation done.]

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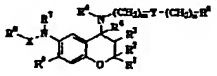
最終頁に続く

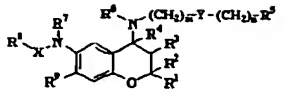
(54)【発明の名称】　ベンゾピラン誘導体

(57)【要約】
【課題】　不整脈治療剤の提供。
【解決手段】　式（Ｉ）
【化１】


(I)

〔式中、R^1及びR^2は、それぞれ独立してC_{1-6}アルキル基等を意味し、R^3は、水酸基又はC_{1-6}アルキルカルボニルオキシ基を意味し、R^4は水素原子を意味するか、又はR^3とR^4が一緒になって結合を意味し、ｍは０～４の整数を意味し、ｎは０～４の整数を意味し、Ｙは存在しないか又は$CR^{11}R^{12}$を意味し、R^5は、アリール基又はヘテロアリール基を意味し、R^6は、水素原子又はC_{1-6}アルキル基を意味し、R^7は、水素原子又はC_{1-6}アルキル基を意味し、Ｘは、存在しないか、又はC=O若しくはSO_2を意味し、R^8は、C_{1-6}アルキル基等を意味し、R^9は、ニトロ基等を意味する。〕により表されるベンゾピラン誘導体又はその医薬的に許容され得る塩を有効成分とする不整脈治療剤の提供。

【特許請求の範囲】
【請求項１】　式（Ｉ）
【化１】



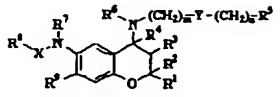
(I)

〔式中、R^1及びR^2は、それぞれ独立して水素原子、C_{1-6}アルキル基（該アルキル基は、ハロゲン原子、C_{1-6}アルコキシ基又は水酸基により任意に置換されていてもよい。）又はフェニル基（該フェニル基は、ハロゲン原子、水酸基、ニトロ基、シアノ基、C_{1-6}アルキル基又はC_{1-6}アルコキシ基により任意に置換されていてもよい。）を意味し、
R^3は、水酸基若しくはC_{1-6}アルキルカルボニルオキシ基を意味するか、又はR^4と一緒になって結合を意味し、
R^4は水素原子を意味するか、又はR^3と一緒になって結合を意味し、
mは０～４の整数を意味し、
nは０～４の整数を意味し、
Yは存在しないか又は$CR^{11}R^{12}$（R^{11}及び、R^{12}はそれぞれ独立して水素原子又はC_{1-6}アルキル基を意味する。）を意味し、
R^5は、アリール基又はヘテロアリール基（該アリール基及びヘテロアリール基は何れもｑ個のR^{10}（R^{10}はハロゲン原子、水酸基、C_{1-6}アルキル基（該アルキル基はハロゲン原子又はC_{1-6}アルコキシ基で置換されていてもよい）、ニトロ基、シアノ基、ホルミル基、ホルムアミド基、アミノ基、C_{1-6}アルキルアミノ基、ジC_{1-6}アルキルアミノ基、C_{1-6}アルキルカルボニルアミノ基、C_{1-6}アルキルスルホニルアミノ基、アミノカルボニル基、C_{1-6}アルキルアミノカルボニル基、ジC_{1-6}アルキルアミノカルボニル基、C_{1-6}アルキルカルボニル基、C_{1-6}アルコキシカルボニル基、アミノスルホニル基、C_{1-6}アルキルスルホニル基、カルボキシル基又はアリールカルボニル基を意味する。）により任意に置換されていてもよい。ｑは１～３の整数を表し、ｑが２又は３の場合、R^{10}は同じでも異なっていてもよい。）を意味し、
R^6は、水素原子又はC_{1-6}アルキル基を意味し、
R^7は、水素原子又はC_{1-6}アルキル基を意味し、
Xは、存在しないか、又はC=O若しくはSO_2を意味し、
R^8は、水素原子、C_{1-6}アルキル基（該アルキル基はハロゲン原子、水酸基又はC_{1-6}アルコキシ基で置換されていてもよい）又はC_{3-6}シクロアルキル基を意味し、R^9は、水素原子、ハロゲン原子、ニトロ基又はシアノ基を意味する。〕により表されるベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項２】　R^1及びR^2が共にメチル基であり、R^3が水酸基であり、R^4が水素原子である請求項１記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項３】　R^9が水素原子又はニトロ基である請求項２記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項４】　XがC=Oであり、R^6及びR^7が共に水素原子である請求項３記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項５】　R^5がベンゼン環であり、Yは存在せず、mが０であり、nが1又は２である請求項４記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項６】　R^8がアルキル基であり、R^9がニトロ基であり、nが２である請求項５記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。
【請求項７】　請求項１記載のベンゾピラン誘導体又はその医薬的に許容され得る塩を有効成分として含有することを特徴とする医薬。
【請求項８】　請求項１記載のベンゾピラン誘導体又はその医薬的に許容され得る塩を有効成分として含有することを特徴とする不整脈治療薬。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、不応期延長作用を有するベンゾピラン誘導体に関するものであり、ヒトを含む哺乳動物に対する不整脈の治療に用いられるものである。
【０００２】
【従来の技術及び発明が解決しようとする課題】ベンゾピラン誘導体としてはクロマカリム（特開昭５８-６７６８３）に代表される４-アシルアミノベンゾピラン誘導体が知られている。これらクロマカリムに代表される４-アシルアミノベンゾピラン誘導体はＡＴＰ感受性K^+チャンネルを開口し、高血圧や喘息の治療に有効であることが知られているが、不応期延長作用に基づく不整脈の治療に関しては言及されていない。ところで、不応期延長作用を主たる機序とする従来の抗不整脈薬（例えばVaughan Williamsによる抗不整脈薬分類の１群薬や、３群に属するｄ－ソタロールなど）は、不応期延長作用と関連のある心室筋活動電位の延長に基づくtorsades de pointes等の突然死を誘発しうる極めて危険な不整脈誘発作用が治療上の課題になっており、より副作用の少ない薬剤が望まれている。本発明者らはこの課題を解決するために、心室筋よりも心房筋に選択的な不応期延長作用を有する化合物の探索研究を実施し、一般式（Ｉ）で表される化合物に、心室筋の不応期および活動電位に影響することなく心房筋に選択的な不応期延長作用があることを見出した。
【０００３】
【課題を解決するための手段】本発明者らは、ベンゾピラン誘導体を鋭意探索した結果、驚くべきことに式（Ｉ）で表される化合物に強い不応期延長作用があり、不整脈治療剤として有用であることを見いだし、本発明を完成した。

【0004】本発明は、式（I）

【0005】

【化2】



(I)

【0006】〔式中、R^1及びR^2は、それぞれ独立して水素原子、C_{1-6}アルキル基（該アルキル基は、ハロゲン原子、C_{1-6}アルコキシ基又は水酸基により任意に置換されていてもよい。）又はフェニル基（該フェニル基は、ハロゲン原子、水酸基、ニトロ基、シアノ基、C_{1-6}アルキル基又はC_{1-6}アルコキシ基により任意に置換されていてもよい。）を意味し、R^3は、水酸基若しくはC_{1-6}アルキルカルボニルオキシ基を意味するか、又はR^4と一緒になって結合を意味し、R^4は水素原子を意味するか、又はR^3と一緒になって結合を意味し、mは0～4の整数を意味し、nは0～4の整数を意味し、Yは存在しないか又は$CR^{11}R^{12}$（R^{11}及び、R^{12}はそれぞれ独立して水素原子又はC_{1-6}アルキル基を意味する。）を意味し、R^5は、アリール基又はヘテロアリール基（該アリール基及びヘテロアリール基は何れもq個のR^{10}（R^{10}はハロゲン原子、水酸基、C_{1-6}アルキル基（該アルキル基はハロゲン原子又はC_{1-6}アルコキシ基で置換されていてもよい）、ニトロ基、シアノ基、ホルミル基、ホルムアミド基、アミノ基、C_{1-6}アルキルアミノ基、ジC_{1-6}アルキルアミノ基、C_{1-6}アルキルカルボニルアミノ基、C_{1-6}アルキルスルホニルアミノ基、アミノカルボニル基、C_{1-6}アルキルアミノカルボニル基、ジC_{1-6}アルキルアミノカルボニル基、C_{1-6}アルキルカルボニル基、C_{1-6}アルコキシカルボニル基、アミノスルホニル基、C_{1-6}アルキルスルホニル基、カルボキシル基又はアリールカルボニル基を意味する。）により任意に置換されていてもよい。qは1～3の整数を表し、qが2又は3の場合、R^{10}は同じでも異なっていてもよい。）を意味し、R^6は、水素原子又はC_{1-6}アルキル基を意味し、R^7は、水素原子又はC_{1-6}アルキル基を意味し、Xは、存在しないか、又はC=O若しくはSO_2を意味し、R^8は、水素原子、C_{1-6}アルキル基（該アルキル基はハロゲン原子、水酸基又はC_{1-6}アルコキシ基で置換されていてもよい）又はC_{3-6}シクロアルキル基を意味し、R^9は、水素原子、ハロゲン原子、ニトロ基又はシアノ基を意味する。〕により表されるベンゾピラン誘導体又はその医薬的に許容され得る塩に関する。

【0007】本発明化合物は、強い不応期延長作用を有し、不整脈治療薬として用いることができる。

【0008】次に、本発明化合物（I）の各置換基を具体的に説明する。なお、本明細書中「n」はノルマルを「i」はイソを、「s」はセカンダリーを、「t」はターシャリーを、「c」はシクロを、「o」はオルトを、「m」はメタを、「p」はパラを意味する。

【0009】C_{1-6}アルキル基としては、メチル、エチル、n-プロピル、i-プロピル、n-ブチル、i-ブチル、s-ブチル、t-ブチル、1-ペンチル、2-ペンチル、3-ペンチル、i-ペンチル、ネオペンチル、2,2-ジメチルプロピル、1-ヘキシル、2-ヘキシル、3-ヘキシル、1-メチル-n-ペンチル、1,1,2-トリメチル-n-プロピル、1,2,2-トリメチル-n-プロピル、3,3-ジメチル-n-ブチル、トリフルオロメチル、トリフルオロエチル、ペンタフルオロエチル、シアノメチル及びヒドロキシメチル等が挙げられる。好ましくは、メチル、エチル、n-プロピル、i-プロピル及びn-ブチルが挙げられる。

【0010】ハロゲン原子としては、フッ素原子、塩素原子、臭素原子及びヨウ素原子が挙げられる。好ましくは、フッ素原子、塩素原子及び臭素原子が挙げられる。

【0011】C_{1-6}アルコキシ基としては、メトキシ、トリフルオロメトキシ、エトキシ、n-プロポキシ、i-プロポキシ、n-ブトキシ、i-ブトキシ、s-ブトキシ、t-ブトキシ、1-ペンチルオキシ、2-ペンチルオキシ、3-ペンチルオキシ、i-ペンチルオキシ、ネオペンチルオキシ、2,2-ジメチルプロポキシ、1-ヘキシルオキシ、2-ヘキシルオキシ、3-ヘキシルオキシ、1-メチル-n-ペンチルオキシ、1,1,2-トリメチル-n-プロポキシ、1,2,2-トリメチル-n-プロポキシ及び3,3-ジメチル-n-ブトキシ等が挙げられる。好ましくは、メトキシ、エトキシ、n-プロポキシ及びi-プロポキシが挙げられる。

【0012】C_{1-6}アルキルカルボニルオキシ基としては、メチルカルボニルオキシ、エチルカルボニルオキシ、n-プロピルカルボニルオキシ、i-プロピルカルボニルオキシ、n-ブチルカルボニルオキシ、i-ブチルカルボニルオキシ、s-ブチルカルボニルオキシ、t-ブチルカルボニルオキシ、1-ペンチルカルボニルオキシ、2-ペンチルカルボニルオキシ、3-ペンチルカルボニルオキシ、i-ペンチルカルボニルオキシ、ネオペンチルカルボニルオキシ、t-ペンチルカルボニルオキシ、1-ヘキシルカルボニルオキシ、2-ヘキシルカルボニルオキシ、3-ヘキシルカルボニルオキシ、1-メチル-n-ペンチルカルボニルオキシ、1,1,2-トリメチル-n-プロピルカルボニルオキシ、1,2,2-トリメチル-n-プロピルカルボニルオキシ及び3,3-ジメチル-n-ブチルカルボニルオキシ等が挙げられる。好ましくは、メチルカルボニルオキシ、エチルカルボニルオキシ、n-プロピルカルボニルオキシ、i-プロピルカルボニルオキシ、n-ブチルカルボニルオキシ及びt-ブチルカルボニルオキシが挙げられる。

【0013】アリール基としては、フェニル、ビフェニリル、ナフチル、アントリル及びフェナントリル等が挙げられる。好ましくは、フェニル、ビフェニリル及びナフチルが挙げられる。

【0014】ヘテロアリール基としては、2-チエニル基、3-チエニル基、2-フリル基、3-フリル基、2-ピラニル基、3-ピラニル基、4-ピラニル基、2-ベンゾフラニル基、3-ベンゾフラニル基、4-ベンゾ

フラニル基、5－ベンゾフラニル基、6－ベンゾフラニル基、7－ベンゾフラニル基、1－イソベンゾフラニル基、4－イソベンゾフラニル基、5－イソベンゾフラニル基、2－ベンゾチエニル基、3－ベンゾチエニル基、4－ベンゾチエニル基、5－ベンゾチエニル基、6－ベンゾチエニル基、7－ベンゾチエニル基、1－イソベンゾチエニル基、4－イソベンゾチエニル基、5－イソベンゾチエニル基、2－クロメニル基、3－クロメニル基、4－クロメニル基、5－クロメニル基、6－クロメニル基、7－クロメニル基、8－クロメニル基、1－ピロリル基、2－ピロリル基、3－ピロリル基、1－イミダゾリル基、2－イミダゾリル基、4－イミダゾリル基、1－ピラゾリル基、3－ピラゾリル基、4－ピラゾリル基、2－チアゾリル基、4－チアゾリル基、5－チアゾリル基、3－イソチアゾリル基、4－イソチアゾリル基、5－イソチアゾリル基、2－オキサゾリル基、4－オキサゾリル基、5－オキサゾリル基、3－イソオキサゾリル基、4－イソオキサゾリル基、5－イソオキサゾリル基、2－ピリジル基、3－ピリジル基、4－ピリジル基、2－ピラジニル基、2－ピリミジニル基、4－ピリミジニル基、5－ピリミジニル基、3－ピリダジニル基、4－ピリダジニル基、1－インドリジニル基、2－インドリジニル基、3－インドリジニル基、5－インドリジニル基、6－インドリジニル基、7－インドリジニル基、8－インドリジニル基、1－イソインドリル基、4－イソインドリル基、5－イソインドリル基、1－インドリル基、2－インドリル基、3－インドリル基、4－インドリル基、5－インドリル基、6－インドリル基、7－インドリル基、1－インダゾリル基、2－インダゾリル基、3－インダゾリル基、4－インダゾリル基、5－インダゾリル基、6－インダゾリル基、7－インダゾリル基、1－プリニル基、2－プリニル基、3－プリニル基、6－プリニル基、7－プリニル基、8－プリニル基、2－キノリル基、3－キノリル基、4－キノリル基、5－キノリル基、6－キノリル基、7－キノリル基、8－キノリル基、1－イソキノリル基、3－イソキノリル基、4－イソキノリル基、5－イソキノリル基、6－イソキノリル基、7－イソキノリル基、8－イソキノリル基、1－フタラジニル基、5－フタラジニル基、6－フタラジニル基、2－ナフチリジニル基、3－ナフチリジニル基、4－ナフチリジニル基、2－キノキサリニル基、5－キノキサリニル基、6－キノキサリニル基、2－キナゾリニル基、4－キナゾリニル基、5－キナゾリニル基、6－キナゾリニル基、7－キナゾリニル基、8－キナゾリニル基、3－シンノリニル基、4－シンノリニル基、5－シンノリニル基、6－シンノリニル基、7－シンノリニル基、8－シンノリニル基、2－プテニジニル基、4－プテニジニル基、6－プテニジニル基、7－プテニジニル基及び3－フラザニル基等が挙げられる。好ましくは、2－ピリジル基、3－ピリジル及び基4－ピリジル基が挙げられる。

【0015】C_{1-6}アルキルアミノ基としては、メチルアミノ、エチルアミノ、n-プロピルアミノ、i-プロピルアミノ、c-プロピルアミノ、n-ブチルアミノ、i-ブチルアミノ、s-ブチルアミノ、t-ブチルアミノ、c-ブチルアミノ、1-ペンチルアミノ、2-ペンチルアミノ、3-ペンチルアミノ、i-ペンチルアミノ、ネオペンチルアミノ、t-ペンチルアミノ、c-ペンチルアミノ、1-ヘキシルアミノ、2-ヘキシルアミノ、3-ヘキシルアミノ、c-ヘキシルアミノ、1-メチル-n-ペンチルアミノ、1,1,2-トリメチル-n-プロピルアミノ、1,2,2-トリメチル-n-プロピルアミノ及び3,3-ジメチル-n-ブチルアミノ等が挙げられる。好ましくは、メチルアミノ、エチルアミノ、n-プロピルアミノ、i-プロピルアミノ及びn-ブチルアミノが挙げられる。

【0016】ジC_{1-6}アルキルアミノ基としては、ジメチルアミノ、ジエチルアミノ、ジ-n-プロピルアミノ、ジ-i-プロピルアミノ、ジ-c-プロピルアミノ、ジ-n-ブチルアミノ、ジ-i-ブチルアミノ、ジ-s-ブチルアミノ、ジ-t-ブチルアミノ、ジ-c-ブチルアミノ、ジ-1-ペンチルアミノ、ジ-2-ペンチルアミノ、ジ-3-ペンチルアミノ、ジ-i-ペンチルアミノ、ジ-ネオペンチルアミノ、ジ-t-ペンチルアミノ、ジ-c-ペンチルアミノ、ジ-1-ヘキシルアミノ、ジ-2-ヘキシルアミノ、ジ-3-ヘキシルアミノ、ジ-c-ヘキシルアミノ、ジ-(1-メチル-n-ペンチル)アミノ、ジ-(1,1,2-トリメチル-n-プロピル)アミノ、ジ-(1,2,2-トリメチル-n-プロピル)アミノ、ジ-(3,3-ジメチル-n-ブチル)アミノ、メチル(エチル)アミノ、メチル(n-プロピル)アミノ、メチル(i-プロピル)アミノ、メチル(c-プロピル)アミノ、メチル(n-ブチル)アミノ、メチル(i-ブチル)アミノ、メチル(s-ブチル)アミノ、メチル(t-ブチル)アミノ、メチル(c-ブチル)アミノ、エチル(n-プロピル)アミノ、エチル(i-プロピル)アミノ、エチル(c-プロピル)アミノ、エチル(n-ブチル)アミノ、エチル(i-ブチル)アミノ、エチル(s-ブチル)アミノ、エチル(t-ブチル)アミノ、エチル(c-ブチル)アミノ、n-プロピル(i-プロピル)アミノ、n-プロピル(c-プロピル)アミノ、n-プロピル(n-ブチル)アミノ、n-プロピル(i-ブチル)アミノ、n-プロピル(s-ブチル)アミノ、n-プロピル(t-ブチル)アミノ、n-プロピル(c-ブチル)アミノ、i-プロピル(c-プロピル)アミノ、i-プロピル(n-ブチル)アミノ、i-プロピル(i-ブチル)アミノ、i-プロピル(s-ブチル)アミノ、i-プロピル(t-ブチル)アミノ、i-プロピル(c-ブチル)アミノ、c-プロピル(n-ブチル)アミノ、c-プロピル(i-ブチル)アミノ、c-プロピル(s-ブチル)アミノ、c-プロピル(t-ブチル)アミノ、c-プロピル(c-ブチル)アミノ、n-ブチル(i-ブチル)アミノ、n-ブチル(s-ブチル)アミノ、n-ブチル(t-ブチル)アミノ、n-ブチル(c-ブチル)アミノ、i-ブチル(s-ブチル)アミノ、i-ブチル(t-ブチル)アミノ、i-ブチル(c-ブチル)アミノ、s-ブチル(t-ブ

チル)アミノ、s-ブチル(c-ブチル)アミノ及びt-ブチル(c-ブチル)アミノ等が挙げられる。好ましくは、ジメチルアミノ、ジエチルアミノ、ジ-n-プロピルアミノ、ジ-i-プロピルアミノ及びジ-n-ブチルアミノが挙げられる。

【００１７】C_{1-6}アルキルカルボニルアミノ基としては、メチルカルボニルアミノ、エチルカルボニルアミノ、n-プロピルカルボニルアミノ、i-プロピルカルボニルアミノ、n-ブチルカルボニルアミノ、i-ブチルカルボニルアミノ、s-ブチルカルボニルアミノ、t-ブチルカルボニルアミノ、1-ペンチルカルボニルアミノ、2-ペンチルカルボニルアミノ、3-ペンチルカルボニルアミノ、i-ペンチルカルボニルアミノ、ネオペンチルカルボニルアミノ、t-ペンチルカルボニルアミノ、1-ヘキシルカルボニルアミノ、2-ヘキシルカルボニルアミノ及び3-ヘキシルカルボニルアミノ等が挙げられる。好ましくは、メチルカルボニルアミノ、エチルカルボニルアミノ、n-プロピルカルボニルアミノ、i-プロピルカルボニルアミノ及びn-ブチルカルボニルアミノが挙げられる。

【００１８】C_{1-6}アルキルスルホニルアミノ基としては、メチルスルホニルアミノ、エチルスルホニルアミノ、n-プロピルスルホニルアミノ、i-プロピルスルホニルアミノ、n-ブチルスルホニルアミノ、i-ブチルスルホニルアミノ、s-ブチルスルホニルアミノ、t-ブチルスルホニルアミノ、1-ペンチルスルホニルアミノ、2-ペンチルスルホニルアミノ、3-ペンチルスルホニルアミノ、i-ペンチルスルホニルアミノ、ネオペンチルスルホニルアミノ、t-ペンチルスルホニルアミノ、1-ヘキシルスルホニルアミノ、2-ヘキシルスルホニルアミノ及び3-ヘキシルスルホニルアミノ等が挙げられる。好ましくは、メチルスルホニルアミノ、エチルスルホニルアミノ、n-プロピルスルホニルアミノ、i-プロピルスルホニルアミノ及びn-ブチルスルホニルアミノが挙げられる。

【００１９】C_{1-6}アルキルアミノカルボニル基としては、メチルアミノカルボニル、エチルアミノカルボニル、n-プロピルアミノカルボニル、i-プロピルアミノカルボニル、n-ブチルアミノカルボニル、i-ブチルアミノカルボニル、s-ブチルアミノカルボニル、t-ブチルアミノカルボニル、1-ペンチルアミノカルボニル、2-ペンチルアミノカルボニル、3-ペンチルアミノカルボニル、i-ペンチルアミノカルボニル、ネオペンチルアミノカルボニル、t-ペンチルアミノカルボニル、1-ヘキシルアミノカルボニル、2-ヘキシルアミノカルボニル及び3-ヘキシルアミノカルボニル等が挙げられる。好ましくは、メチルアミノカルボニル、エチルアミノカルボニル、n-プロピルアミノカルボニル、i-プロピルアミノカルボニル及びn-ブチルアミノカルボニルが挙げられる。

【００２０】ジC_{1-6}アルキルアミノカルボニル基としては、ジメチルアミノカルボニル、ジエチルアミノカルボニル、ジ-n-プロピルアミノカルボニル、ジ-i-プロピルアミノカルボニル、ジ-c-プロピルアミノカルボニル、ジ-n-ブチルアミノカルボニル、ジ-i-ブチルアミノカルボニル、ジ-s-ブチルアミノカルボニル、ジ-t-ブチルアミノカルボニル、ジ-c-ブチルアミノカルボニル、ジ-1-ペンチルアミノカルボニル、ジ-2-ペンチルアミノカルボニル、ジ-3-ペンチルアミノカルボニル、ジ-i-ペンチルアミノカルボニル、ジ-ネオペンチルアミノカルボニル、ジ-t-ペンチルアミノカルボニル、ジ-c-ペンチルアミノカルボニル、ジ-1-ヘキシルアミノカルボニル、ジ-2-ヘキシルアミノカルボニル及びジ-3-ヘキシルアミノカルボニル等が挙げられる。好ましくは、ジメチルアミノカルボニル、ジエチルアミノカルボニル、ジ-n-プロピルアミノカルボニル、ジ-i-プロピルアミノカルボニル、ジ-c-プロピルアミノカルボニル及びジ-n-ブチルアミノカルボニルが挙げられる。

【００２１】C_{1-6}アルキルカルボニル基としては、メチルカルボニル、エチルカルボニル、n-プロピルカルボニル、i-プロピルカルボニル、n-ブチルカルボニル、i-ブチルカルボニル、s-ブチルカルボニル、t-ブチルカルボニル、1-ペンチルカルボニル、2-ペンチルカルボニル、3-ペンチルカルボニル、i-ペンチルカルボニル、ネオペンチルカルボニル、t-ペンチルカルボニル、1-ヘキシルカルボニル、2-ヘキシルカルボニル及び3-ヘキシルカルボニルが挙げられる。好ましくは、メチルカルボニル、エチルカルボニル、n-プロピルカルボニル、i-プロピルカルボニル及びn-ブチルカルボニルが挙げられる。

【００２２】C_{1-6}アルコキシカルボニル基としては、メトキシカルボニル、エトキシカルボニル、n-プロポキシカルボニル、i-プロポキシカルボニル、n-ブトキシカルボニル、i-ブトキシカルボニル、s-ブトキシカルボニル、t-ブトキシカルボニル、1-ペンチルオキシカルボニル、2-ペンチルオキシカルボニル、3-ペンチルオキシカルボニル、i-ペンチルオキシカルボニル、ネオペンチルオキシカルボニル、t-ペンチルオキシカルボニル、1-ヘキシルオキシカルボニル、2-ヘキシルオキシカルボニル及び3-ヘキシルオキシカルボニル等が挙げられる。好ましくは、メトキシカルボニル、エトキシカルボニル、n-プロポキシカルボニル、i-プロポキシカルボニル、n-ブトキシカルボニル、i-ブトキシカルボニル、s-ブトキシカルボニル及びt-ブトキシカルボニルが挙げられる。

【００２３】C_{1-6}アルキルスルホニル基としては、メタンスルホニル及びエタンスルホニルが挙げられる。

【００２４】アリールカルボニル基としては、ベンゾイル、p-メチルベンゾイル、p-t-ブチルベンゾイル、p-メトキシベンゾイル、p-クロルベンゾイル、p-ニトロベンゾイル及びp-シアノベンゾイルが挙げられる。好ましくは、ベンゾイル、p-ニトロベンゾイル及びp-シアノベンゾイルが挙げられる。

【００２５】C_{3-6}シクロアルキル基としては、シクロプロピル、シクロブチル、シクロペンチル、シクロヘキシ

ル、シクロヘプチル及びシクロオクチル等が挙げられる。好ましくは、シクロプロピル、シクロブチル及びシクロヘキシルが挙げられる。

【００２６】本発明に用いられる好ましい化合物としては、以下に示す化合物が挙げられる。

【００２７】（１）R^1及びR^2が共にメチル基であり、R^3が水酸基であり、R^4が水素原子である式（Ｉ）で表されるベンゾピラン誘導体又はその医薬的に許容され得る塩。

【００２８】（２）R^9が水素原子又はニトロ基である上記（１）記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。

【００２９】（３）Ｘが$C=O$であり、R^6及びR^7が共に水素原子である上記（２）記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。

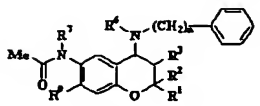
【００３０】（４）R^5がベンゼン環であり、Ｙは存在せず、ｍが０であり、ｎが1又は２であるである上記（３）記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。

【００３１】（５）R^8が、アルキル基であり、R^9がニトロ基であり、ｎが２である上記（４）記載のベンゾピラン誘導体又はその医薬的に許容され得る塩。

【００３２】以下に、本発明に用いることができる化合物の具体例を示すが、本発明はこれらに制限されるものではない。なお、「Ｍｅ」はメチル基を、「Ｅｔ」はエチル基を、「Ｐｒ」はプロピル基を、「Ｂｕ」はブチル基を、「Ａｃ」はアセチル基（$COCH_3$）を、「－」は結合をそれぞれ意味する。

【００３３】

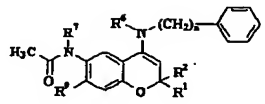
【化３】



R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	3
Me	Me	OH	H	H	NO_2	4
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

【００３４】

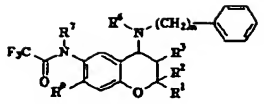
【化４】



R^1	R^2	R^6	R^7	R^9	n
H	H	H	H	H	0
Me	Me	Me	H	H	1
Me	Me	Et	H	H	2
Me	Me	n-Pr	H	H	3
Me	Me	i-Pr	H	H	4
Me	Me	n-Bu	H	H	0
Me	Me	i-Bu	H	H	1
Me	Me	t-Bu	H	H	2
Me	Me	n-Pen	H	H	3
Me	Me	n-Hex	H	H	4
Me	Me	H	H	H	2
Me	Me	Me	H	H	2
Me	Me	Et	H	H	3
Me	Me	H	H	H	2
Me	Me	H	H	NO_2	2
Me	Me	H	Me	NO_2	1
Me	Me	H	Et	NO_2	2
Me	Me	H	n-Pr	NO_2	3
Ph	Ph	H	i-Pr	NO_2	4
Et	Et	H	n-Bu	NO_2	2
n-Pr	n-Pr	H	i-Bu	NO_2	2
i-Pr	i-Pr	H	t-Bu	NO_2	2
n-Bu	n-Bu	H	n-Pen	NO_2	2
i-Bu	i-Bu	H	n-Hex	NO_2	2
t-Bu	t-Bu	H	Me	NO_2	3
n-Pen	n-Pen	H	H	Cl	3
n-Hex	n-Hex	H	H	F	3
CF_3	CF_3	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	H	H	CN	3

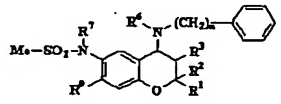
【００３５】

【化５】



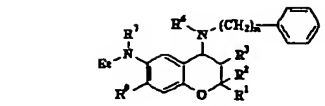
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

【0036】
【化6】



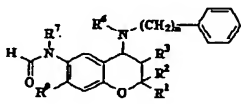
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

【0037】
【化7】



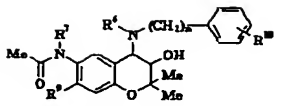
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

【0038】
【化8】



R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

【0039】
【化9】



R^8	R^7	R^6	R^{10}	n
H	H	H	p-MeO	0
Me	H	H	p-MeO	1
H	H	NO_2	p-MeO	2
n-Pr	H	H	p-MeO	3
i-Pr	H	H	p-MeO	4
n-Bu	H	H	m-MeO	0
i-Bu	H	H	o-MeO	1
t-Bu	H	H	p-Me	2
n-Pen	H	H	p-Et	3
n-Hex	H	H	m-Et	4
H	H	H	o-Et	2
H	H	NO_2	p-Cl	2
Et	H	H	p-F	3
H	H	NO_2	p-OH	2
H	H	NO_2	p-OH	2
H	Me	NO_2	p-NO_2	1
H	Et	NO_2	p-CN	2
H	n-Pr	NO_2	p-NMe_2	3
H	i-Pr	NO_2	p-NHMe	4
H	n-Bu	NO_2	p-CO_2H	2
H	i-Bu	NO_2	m-CO_2Et	2
H	t-Bu	NO_2	m-OMe	2
H	H	NO_2	p-NO_2	2
H	n-Hex	NO_2	p-NMe_2	2
H	Me	NO_2	p-NHMe	3
H	H	NO_2	p-NH_2	2
H	H	F	p-Et	3
H	H	Br	p-Pr	3
H	H	CN	p-CH_2OMe	3

【００４０】本発明化合物は、３位と４位に不斉炭素を有しており、該不斉炭素に基づく光学異性体が存在するが、ラセミ体と同様に光学活性体も本発明の用途に用いることができる。又、３位と４位の立体配置に基づくシス又はトランス異性体も包含するが、好ましくはトランス異性体である。

【００４１】又、塩の形成可能な化合物であるときはその医薬的に許容し得る塩も有効成分として用いることができる。医薬的に許容し得る塩としては塩酸塩、臭化水素酸塩、硫酸塩、メタンスルホン酸塩、酢酸塩、安息香酸塩、酒石酸塩、リン酸塩、乳酸塩、マレイン酸塩、フマル酸塩、リンゴ酸塩、グルコン酸塩及びサリチル酸塩等が挙げられる。好ましくは、塩酸塩及びメタンスルホン酸塩が挙げられる。

【００４２】

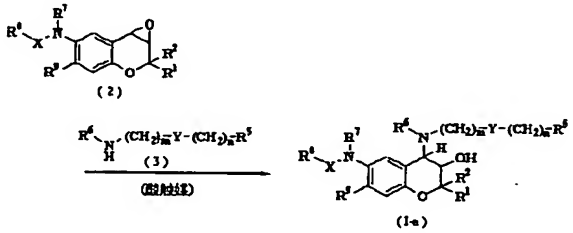
【発明の実施の形態】

【００４３】次に本発明化合物の製法を説明する。

【００４４】一般式（Ｉ）によって表される化合物のうち、R^4が水素原子であり、R^3が水酸基である、（Ｉ－ａ）で表される化合物は、下記の反応式によって示されるように、一般式（２）により表される化合物と化合物（３）を不活性溶媒中反応させることにより得ることができる。一般式（２）により表される化合物は、既知の方法（J. M. Evansら、J. Med. Chem. 1984, 27, 1127、J. Med. Chem. 1986, 29, 2194、J. T. NorthらJ. Org. Chem. 1995, 60, 3397や、特開昭５６－５７７８５号公報、特開昭５６－５７７８６号公報、特開昭５８－１８８８８０号公報、特開平２－１４１号公報、特開平１０－８７６５０号広報及び特開平１１－２０９３６６号広報等に記載の方法）に従って合成することができる。

【００４５】

【化１０】



【００４６】一般式（２）によって表される化合物と化合物（３）の反応に用いる溶媒としては下記のものが挙げられる。ジメチルスルホキシドによって代表されるスルホキシド系溶媒、ジメチルホルムアミド又はジメチルアセトアミドによって代表されるアミド系溶媒、エチルエーテル、ジメトキシエタン又はテトラヒドロフランによって代表されるエーテル系溶媒、ジクロロメタン、クロロホルム、ジクロロエタンによって代表されるハロゲン系溶媒、アセトニトリル、プロピオニトリルによって代表されるニトリル系溶媒、ベンゼン、トルエンによって代表される芳香族炭化水素系溶媒、ヘキサン、ヘプタンによって代表される炭化水素系溶媒、酢酸エチルによって代表されるエステル系溶媒が挙げられる。又、無溶媒の条件で反応を行うこともできる。好ましくはエーテル系溶媒とニトリル系溶媒が挙げられる。

【００４７】反応温度は、通常－８０℃から用いられる反応溶媒の還流温度までであり、好ましくは、－１０℃～１００℃である。

【００４８】反応原料のモル比は、化合物（３）／化合物（２）は０．５～２０．０の範囲であり、好ましくは１．０～１０．０の範囲である。

【００４９】反応には酸触媒を用いてもよい。

【００５０】用いる酸触媒としては、塩酸、硫酸に代表される無機酸、塩化アルミニウム、四塩化チタン、三フッ化ホウ素ジエチルエーテル錯体、過塩素酸、過塩素酸リチウム、臭化リチウム、トリフルオロメタンスルホン酸イッテルビウムに代表されるルイス酸等が挙げられる。

【００５１】好ましくは、臭化リチウム、過塩素酸、過塩素酸リチウムが挙げられる。

【００５２】一般式（Ｉ）によって表される化合物のうち、（Ｉ－ａ）で表される化合物に含まれないもの（R^3とR^4が一緒になって結合を意味する化合物及びR^4が水素原子でありR^3がC_{1-6}アルキルカルボニルオキシ基である化合物）は、特開昭５２－９１８６６号公報及び特開平１０－８７６５０号公報等に記載の製造法と同様な方法により製造することができる。

【００５３】一般式（I）により表される化合物のうち光学活性体の合成は、ラセミ体を光学分割する方法（特

開平3－141286号公報、米国特許5097037号及び欧州特許409165号）を利用することにより達成される。　又、一般式（2）により表される化合物の光学活性体の合成は、不斉合成による方法（特表平5－507645号公報、特開平5－301878号公報、特開平7－285983号公報、欧州特許535377号公開公報及び米国特許5420314号）を利用することにより達成される。

【0054】前述したように、本発明者らは一般式（I）で表わされる化合物には強い不応期延長作用を有していることを見い出した。不応期延長作用は抗不整脈作用の奏功機序の1つであり，臨床の不整脈に対する有効性を外挿しうる重要な指標である。不応期延長作用を主たる機序とする従来の抗不整脈薬（例えばVaughan Williamsによる抗不整脈薬分類の第3群に属するd－ソタロールなど）は，不応期延長作用と関連のある心室筋活動電位の延長に基づくtorsades de pointes等の突然死を誘発しうる極めて危険な不整脈誘発作用が重大な課題とされており，心房筋が主体の不整脈（上室性頻拍症，心房粗動，心房細動など）に対する治療の問題になっている。この課題を解決するために本発明者らは，心室筋よりも心房筋に選択的な不応期延長作用を有する化合物の探索研究を実施し，一般式（I）で表される化合物に，心室筋の不応期および活動電位に影響することなく心房筋に選択的な不応期延長作用があることを見出した。本発明者らの発見の既存技術との違いは，これらの化合物群に対して心房筋に選択的な不応期延長作用を付与し得たところにあり，このことは，摘出した心室筋の活動電位持続時間に影響しないこと，および麻酔動物の心電図QTに影響を及ぼさないことによっても示されている。以上のことから，本化合物は心室筋における不整脈誘発作用を持ち合わせず，既存技術に比べて心房筋が主体の不整脈においてより安全な使用に貢献できる可能性を提供しうるものである。この技術は，心房性不整脈に係わる，例えば発作性，慢性，手術前，手術中あるいは手術後の抗心房細動剤，抗心房粗動剤，抗心房性頻脈剤としての治療あるいは予防的な利用；心房性不整脈に基づく塞栓症への進展予防，心房性不整脈あるいは頻脈を原因とする心室性不整脈あるいは頻脈への移行の予防，心室性不整脈あるいは頻脈に移行しうる心房性不整脈あるいは頻脈予防作用に基づく生命予後悪化の予防の目的として有用である。

【0055】本発明は、これらの治療に一般式（I）で表わされる化合物の有効な量を含む医薬組成物又は獣医薬組成物を提供する。

【0056】本発明に係る化合物の投与形態としては、注射剤（皮下、静脈内、筋肉内、腹腔内注射）、軟膏剤、坐剤、エアゾール剤等による非経口投与又は錠剤、カプセル剤、顆粒剤、丸剤、シロップ剤、液剤、乳剤、懸濁液剤等による経口投与をあげることができる。

【0057】本発明に係る化合物を含有する上記の医薬的又は獣医薬的組成物は、全組成物の重量に対して、本発明に係る化合物を約0.01～99.5%、好ましくは、約0.1～30%を含有する。

【0058】本発明に係る化合物に又は該化合物を含有する組成物に加えて、他の医薬的に又は獣医薬的に活性な化合物を含ませることができる。また、これらの組成物は、本発明に係る化合物の複数を含ませることができる。

【0059】本発明化合物の臨床的投与量は、年令、体重、患者の感受性、症状の程度等により異なるが、通常効果的な投与量は、成人一日0.003～1.5g、好ましくは、0.01～0.6g程度である。しかし必要により上記の範囲外の量を用いることもできる。

【0060】本発明化合物は、製薬の慣用手段によって投与用に製剤化される。即ち、経口投与用の錠剤、カプセル剤、顆粒剤、丸剤は、賦形剤、例えば白糖、乳糖、ブドウ糖、でんぷん、マンニット；結合剤、例えばヒドロキシプロピルセルロース、シロップ、アラビアゴム、ゼラチン、ソルビット、トラガント、メチルセルロース、ポリビニルピロリドン；崩壊剤、例えばでんぷん、カルボキシメチルセルロース又はそのカルシウム塩、微結晶セルロース、ポリエチレングリコール；滑沢剤、例えばタルク、ステアリン酸マグネシウム又はカルシウム、シリカ；潤滑剤、例えばラウリル酸ナトリウム、グリセロール等を使用して調製される。

【0061】注射剤、液剤、乳剤、懸濁剤、シロップ剤及びエアゾール剤は、活性成分の溶剤、例えば水、エチルアルコール、イソプロピルアルコール、プロピレングリコール、1,3－ブチレングリコール、ポリエチレングリコール；界面活性剤、例えばソルビタン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、ポリオキシエチレン脂肪酸エステル、水素添加ヒマシ油のポリオキシエチレンエーテル、レシチン；懸濁剤、例えばカルボキシメチルナトリウム塩、メチルセルロース等のセルロース誘導体、トラガント、アラビアゴム等の天然ゴム類；保存剤、例えばパラオキシ安息香酸のエステル、塩化ベンザルコニウム、ソルビン酸塩等を使用して調製される。

【0062】経皮吸収型製剤である軟膏には、例えば白色ワセリン、流動パラフィン、高級アルコール、マクロゴール軟膏、親水軟膏、水性ゲル基剤等が用いられる。坐剤は、例えばカカオ脂、ポリエチレングリコール、ラノリン、脂肪酸トリグリセライド、ココナット油、ポリソルベート等を使用して調製される。

【0063】

【実施例】以下、本発明を実施例にて詳述するが、本発明は、これらの実施例に何ら限定されるものではない。

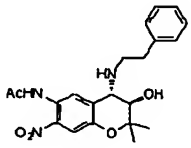
〔合成例〕

【0064】合成例1

トランス-6-アセチルアミノ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-4-(2-フェネチルアミノ)-2H-1-ベンゾピラン-3-オール

【0065】

【化11】



【0066】6-アセチルアミノ-3,4-エポキシ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-2H-1-ベンゾピラン (500 mg, 1.80 mmol) と過塩素酸リチウム (766mg, 7.20 mmol) のテトラヒドロフラン溶液(15 mL) に室温で 2-フェネチルアミン (904 μL, 7.20 mmol) を加え、65 ℃で 9 時間撹拌した。酢酸エチルを加え、有機相を飽和塩化アンモニウム水溶液で2回、飽和食塩水で1回洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残査を中圧カラムクロマトグラフィー (ヘキサン : 酢酸エチル = 1 : 1) で精製した後、ヘキサン-酢酸エチルで再結晶し、目的物を黄色結晶として得た (収率 61 %)。

【0067】mp. : 172-174 ° C

^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.48 (s, 3H), 1.60 (br s, 2H), 2.28 (s,3H), 2.83 (t, J = 7.0 Hz, 2H), 2.85-3.00 (m, 2H), 3.47 (d, A part of AB,J = 10.3 Hz, 1H), 3.67 (d, B part of AB, J = 10.3 Hz, 1H), 7.21-7.33 (m, 5H), 7.60 (s, 1H), 8.59 (s, 1H), 9.96 (s, 1H).

MS (EI) m / z; 400[M+1]$^+$, 327 (bp).

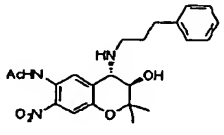
【0068】同様の方法により下記の化合物を得た。(合成例2～36)

【0069】合成例2

トランス-6-アセチルアミノ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-4-(3-フェニルプロピルアミノ)-2H-1-ベンゾピラン-3-オール

【0070】

【化12】



【0071】収率 71 %

^{1}H-NMR ($CDCl_3$) δ:1.21 (s, 3H), 1.51 (s, 3H), 1.87 (quint, J = 7.4 Hz, 2H), 1.94 (br s, 2H), 2.27 (s, 3H), 2.63-2.73 (m, 4H), 3.54 (d, A part ofAB, J = 10.3 Hz, 1H), 3.71 (d, B part of AB, J = 10.3 Hz, 1H), 7.16-7.23(m, 3H), 7.25-7.27 (m, 2H), 7.63 (s, 1H), 8.68 (s, 1H), 10.02 (s, 1H).

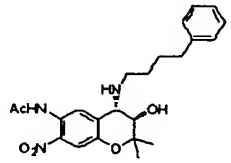
MS (EI) m / z; 413[M]$^+$, 221 (bp).

【0072】合成例3

トランス-6-アセチルアミノ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-4-(4-フェニルブチルアミノ)-2H-1-ベンゾピラン-3-オール

【0073】

【化13】



【0074】収率 50 %

^{1}H-NMR ($CDCl_3$) δ:1.20 (s, 3H), 1.52 (s, 3H), 1.55-1.60 (m, 2H), 1.63-1.75 (m, 2H), 2.25 (s, 3H), 2.40 (br s, 2H), 2.62 (t, J = 7.4 Hz, 2H), 2.58-2.72 (m, 2H), 3.57 (d, A part of AB, J = 10.0 Hz, 1H), 3.70 (d, B partof AB, J = 10.0 Hz, 1H), 7.15-7.18 (m, 3H), 7.24-7.62 (m, 2H), 7.62 (s,1H), 8.67 (s, 1H), 10.00 (s, 1H).

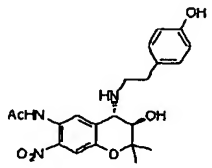
MS (EI) m / z; 427[M]$^+$, 150 (bp).

【0075】合成例4

トランス-6-アセチルアミノ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-4-[2-(4-ヒドロキシフェニル)エチルアミノ]-2H-1-ベンゾピラン-3-オール

【0076】

【化14】



【0077】収率 29 %

^{1}H-NMR ($CDCl_3$) δ:1.17 (s, 3H), 1.48 (s, 3H), 2.00 (br s, 3H), 2.29 (s, 3H), 2.70-2.85 (m, 3H), 2.86-2.95 (m, 1H), 3.51 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, B part of AB, J = 10.3 Hz, 1H), 6.77 (d, J = 8.4 Hz,2H), 7.06 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 8.46 (s, 1H), 9.95 (s, 1H).

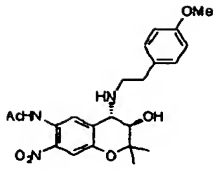
MS (EI) m / z; 416[M+1]$^+$, 308 (bp).

【0078】合成例5

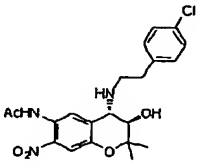
トランス-6-アセチルアミノ-3,4-ジヒドロ-2,2-ジメチル-7-ニトロ-4-[2-(4-メトキシフェニル)エチルアミノ]-2H-1-ベンゾピラン-3-オール

【0079】

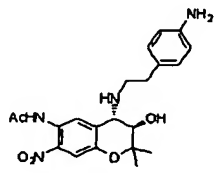
【化15】



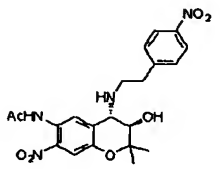
【００８０】収率 18 %
^{1}H-NMR ($CDCl_3$) δ:1.18 (s, 3H), 1.49 (s, 3H), 1.80 (br s, 2H), 2.27 (s, 3H), 2.76-3.00 (m, 4H), 3.56 (d, A part of AB, J = 10.5 Hz, 1H), 3.77 (d,B part of AB, J = 10.5 Hz, 1H), 3.79 (s, 3H), 6.83 (d, J = 8.6 Hz, 2H),7.23 (d, J = 8.6 Hz, 2H), 7.61 (s, 1H), 8.55 (s, 1H), 9.93 (s, 1H) .
MS (EI) m / z; 430[M+1]$^+$, (bp).
【００８１】合成例6
トランス−6−アセチルアミノ−3, 4−ジヒドロ−2, 2−ジメチル−7−ニトロ−４− [2− (4−クロロフェニル) エチルアミノ] −2H−1−ベンゾピラン−3−オール
【００８２】
【化１６】



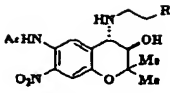
【００８３】収率 66 %
^{1}H-NMR ($CDCl_3$) δ:1.18 (s, 3H), 1.49 (s, 3H), 1.70 (br s, 2H), 2.28 (s, 3H), 2.78 (t, J = 6.8 Hz, 2H), 2.84-2.99 (m, 2H), 3.50 (d, A part of AB,J = 10.2 Hz, 1H), 3.68 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.17(d, J= 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 8.59 (s, 1H), 9.97 (s, 1H).
MS (EI) m / z; 434[M+1]$^+$, 361 (bp).
【００８４】合成例7
トランス−6−アセチルアミノ−3, 4−ジヒドロ−2, 2−ジメチル−7−ニトロ−４− [2− (4−アミノフェニル) エチルアミノ] −2H−1−ベンゾピラン−3−オール
【００８５】
【化１７】

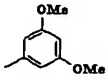
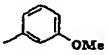


【００８６】収率 40 %
^{1}H-NMR ($CDCl_3$) δ:1.17 (s, 3H), 1.48 (s, 3H), 1.69 (br s, 4H), 2.28 (s, 3H), 2.71 (t, J = 6.8 Hz, 2H), 2.79-2.92 (m, 2H), 3.48 (d, A part of AB,J = 10.3 Hz, 1H), 3.67 (dd, B part of AB, J = 10.3 and 1.1 Hz, 1H), 6.63(d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.60 (s, 1H), 8.58 (s, 1H), 9.96 (s, 1H).
MS (EI) m / z; 415[M+1]$^+$, 237(bp).
【００８７】合成例8
トランス−6−アセチルアミノ−3, 4−ジヒドロ−2, 2−ジメチル−7−ニトロ−４− [2− (4−ニトロフェニル) エチルアミノ] −2H−1−ベンゾピラン−3−オール
【００８８】
【化１８】

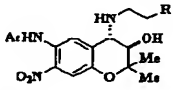


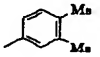
【００８９】収率 19 %
mp.: 211-213 ° C (decomposition)
^{1}H-NMR (DMSO-d_6) δ: 1.15 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 3.05-3.40(m, 5H), 4.06 (m 1H), 4.51 (m, 1H), 6.44 (s, 1H), 7.40 (s, 1H), 7.56 (d,J = 8.8 Hz, 2H), 7.90 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 10.14 (s, 1H).
MS (EI) m / z; 444[M]$^+$, 371 (bp).
【００９０】合成例９〜３６
【００９１】
【化１９】



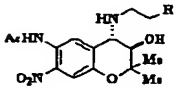
化合物No.	R
合成例9	
合成例10	
合成例11	
合成例12	
合成例13	
合成例14	
合成例15	

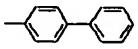
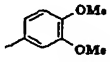
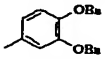
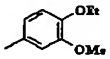
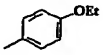
【0092】
【化20】



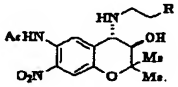
化合物No.	R
合成例16	
合成例17	
合成例18	
合成例19	
合成例20	
合成例21	
合成例22	

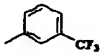
【0093】
【化21】



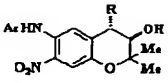
化合物No.	R
合成例23	
合成例24	
合成例25	
合成例26	
合成例27	
合成例28	
合成例29	

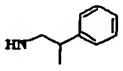
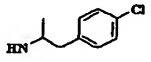
【0094】
【化22】



化合物No.	R
合成例30	
合成例31	
合成例32	
合成例33	

【0095】
【化23】



化合物No.	R
合成例34	
合成例35	
合成例36	

【0096】合成例9

【0097】赤色結晶
mp. : 176.5-178.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.86-2.98 (m, 4H), 3.46 (d, J = 10.0 Hz, 1H), 3.68 (d, J = 10.0 Hz, 1H), 7.00-7.10 (m, 2H), 7.17-7.26 (m, 2H), 7.61 (s, 1H), 8.63 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 418[M+1]$^+$, 346, 309, 179 (bp).
【0098】合成例10
【0099】赤色結晶
mp. : 163.5-165.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.81-2.99 (m, 4H), 3.49 (d, J = 10.1 Hz, 1H), 3.68 (d, J = 10.1 Hz, 1H), 6.89-6.95 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 7.23-7.26 (m, 1H), 7.61 (s, 1H), 8.58(s, 1H), 9.96 (s, 1H).
MS (EI) m / z; 418[M+1]$^+$, 344, 298 (bp).
【0100】合成例11
【0101】橙色結晶
mp. : 141.0-142.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.78-2.97 (m, 4H), 3.49 (d, J = 10.1 Hz, 1H), 3.68 (d, J = 10.1 Hz, 1H), 6.99 (t, J= 8.8 Hz, 2H), 7.19 (dd, J = 2.9, 5.5 Hz, 2H), 7.61 (s, 1H), 8.57 (s, 1H), 9.97 (s, 1H).
MS (EI) m / z; 417[M]$^+$, 345, 302, 176 (bp).
【0102】合成例12
【0103】黄色結晶
mp. : 151.0-152.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), 2.77 (t, J =6.8 Hz, 2H), 2.87-2.97 (m, 2H), 3.51 (d, J = 10.1 Hz, 1H), 3.69 (d, J =10.1 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 2H), 7.60(s, 1H), 8.55 (s, 1H), 9.93 (s, 1H).
MS (EI) m / z; 459[M]$^+$, 441, 307, 278, 193 (bp).
【0104】合成例13
【0105】赤色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.78-2.97 (m, 4H), 3.50 (d, J = 10.1 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H),3.79 (s, 3H), 6.75-6.83 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.60 (s, 1H), 8.56 (s, 1H), 9.94 (s, 1H).
MS (FAB) m / z; 430[M+1]$^+$ (bp).
【0106】合成例14
【0107】赤色結晶
mp. : 171.5-172.8 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.86-2.98 (m, 4H), 3.48 (d, J = 10.4 Hz, 1H), 3.70 (d, J = 10.4 Hz, 1H), 7.14-7.22 (m, 2H), 7.26-7.28 (m, 1H), 7.34 (dd, J = 1.6, 7.6 Hz, 1H), 7.61 (s, 1H),8.64 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 433[M+1]$^+$, 357, 318(bp).
【0108】合成例15
【0109】黄色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.79 (t, J =6.9 Hz, 2H), 2.86-2.98 (m, 2H), 3.50 (d, J = 10.1 Hz, 1H), 3.68 (d, J =10.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.61(s, 1H), 8.60 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 481[M+2]$^+$, 479[M]$^+$, 406 (bp).
【0110】合成例16
【0111】橙色結晶
mp. : 90.0-91.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.48 (s, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.75-2.78 (m, 2H), 2.88-2.91 (m, 2H), 3.50 (d, J = 10.1Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.60 (s, 1H), 8.61 (s, 1H), 9.97 (s, 1H).
MS (EI) m / z; 428[M+1]$^+$, 356 (bp).
【0112】合成例17
【0113】茶色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.16 (s, 3H), 1.48 (s, 3H), 2.29 (s, 3H), 2.82 (brs, 1H), 3.25 (dd, J = 2.1, 7.7 Hz, 2H), 3.52 (d, J = 10.3 Hz, 1H), 3.69 (d,J = 10.3 Hz, 1H), 7.18-7.35 (m, 10H), 7.61 (s, 1H), 8.61 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 475[M+1]$^+$, 310, 280 (bp).
【0114】合成例18
【0115】黄色結晶
mp. 186.0-188.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.49 (s, 3H),2.27 (s, 3H), 2.78-3.02 (m, 4H), 3.55 (d, J = 10.3 Hz, 1H), 3.76 (d, J =10.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 6.76-6.82 (m, 3H), 7.61 (s, 1H), 8.53 (s, 1H), 9.93 (s, 1H).
MS (EI) m / z; 473[M+1]$^+$, 440, 401, 308 (bp).
【0116】合成例19
【0117】茶色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.84-2.95 (m, 4H), 3.51 (d, J = 10.4 Hz, 1H), 3.71 (d, J = 10.4 Hz, 1H), 7.18 (dd, J= 2.0, 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H),7.61 (s, 1H), 8.63 (s, 1H), 9.99 (s, 1H).
MS (EI) m / z; 468[M]$^+$, 396, 353 (bp).
【0118】合成例20
【0119】赤色結晶
mp. : 156.0-157.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.50 (s, 3H), 2.28

(s, 3H), 2.93-3.04 (m, 4H), 3.52 (d, J = 10.1 Hz, 1H), 3.71 (d, J = 10.1 Hz, 1H), 6.88 (d, J= 3.3 Hz, 1H), 6.95 (dd, J = 3.3, 5.1 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H),7.62 (s, 1H), 8.64 (s, 1H), 9.98 (s, 1H).

MS (EI) m / z; 405[M]$^+$, 332, 308 (bp).

【0120】合成例21

【0121】茶色結晶

mp. : 172.0-174.0 ° C

^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.84 (t, J =6.6 Hz, 2H), 2.90-3.03 (m, 2H), 3.53 (d, J = 10.1 Hz, 1H), 3.71 (d, J =10.1 Hz, 1H), 7.18 (d, J = 5.9 Hz, 2H), 7.62 (s, 1H), 8.49 (d, J = 5.9Hz, 2H), 8.64 (s, 1H), 9.98 (s, 1H).

MS (FAB) m / z; 401[M+1]$^+$, 171, 157 (bp).

【0122】合成例22

【0123】茶色非晶質

^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.80-2.87 (m, 3H), 2.93-2.96 (m, 1H), 3.58 (d, J = 10.3 Hz, 1H), 3.75 (d, J = 10.3 Hz, 1H), 7.24 (m, 1H), 7.60 (s, 1H), 7.62 (d, J = 1.5 Hz, 1H), 8.42 (t, J= 1.5 Hz, 2H), 8.67 (s, 1H), 9.96 (s, 1H).

MS (EI) m / z; 400[M]$^+$, 328, 280 (bp).

【0124】合成例23

【0125】橙色結晶

mp. : 147.0-149.0 ° C

^{1}H-NMR ($CDCl_3$) δ: 1.24 (s, 3H), 1.54 (s, 3H), 2.26 (s, 3H), 2.94-3.07 (m, 2H), 3.19-3.21 (m, 2H), 3.66 (d, J = 10.1 Hz, 1H), 3.76 (d, J = 10.1 Hz, 1H), 7.16-7.19 (m, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.58 (s, 1H), 7.63-7.68 (m, 1H), 8.53 (s, 1H), 8.71 (s, 1H), 9.94 (s, 1H).

MS (FAB) m / z; 400[M]$^+$, 366, 328, 120 (bp).

【0126】合成例24

【0127】茶色非晶質

^{1}H-NMR ($CDCl_3$) δ: 1.14 (s, 3H), 1.45 (s, 3H), 2.24 (s, 3H), 2.91-3.02 (m, 4H), 3.51 (d, J = 10.3 Hz, 1H), 3.67 (d, J = 10.3 Hz, 1H), 7.10 (t, J= 7.0 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.37(d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 8.10 (brs,1H), 8.43 (s, 1H), 9.82 (s, 1H).

MS (FAB) m / z; 437[M-1]$^+$, 307, 278, 233, 194 (bp).

【0128】合成例25

【0129】茶色非晶質

^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 2.23 (s, 3H), 2.87 (t, J =6.8 Hz, 2H), 2.94-2.99 (m, 2H), 3.52 (d, J = 10.1 Hz, 1H), 3.70 (d, J =10.1 Hz, 1H), 7.30-7.35 (m, 3H), 7.41-7.45 (m, 2H), 7.52-7.59 (m, 4H),7.60 (s, 1H), 8.61 (s, 1H), 9.96 (s, 1H).

MS (EI) m / z; 475[M]$^+$, 442, 401 (bp).

【0130】合成例26

【0131】赤色非晶質

^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), 2.76-2.79 (m, 2H), 2.84-2.90 (m, 1H), 2.93-2.98 (m, 1H), 3.53 (d, J = 10.1 Hz, 1H),3.70 (d, J = 10.1 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.76-6.81 (m, 3H), 7.60 (s, 1H), 8.54 (s, 1H), 9.93 (s, 1H).

MS (EI) m / z; 460[M+1]$^+$, 237, 165 (bp).

【0132】合成例27

【0133】58 % 収率

黄色結晶

mp. 225 ° C

^{1}H-NMR (DMSO-d_6) δ: 1.15 (s, 3H), 1.45 (s, 3H), 2.04 (s, 3H), 2.90-3.10(m, 5H), 3.21 (br s, 1H), 4.00-4.05 (m, 1H), 4.47-4.51 (m, 1H), 5.09 (s,2H), 5.12 (s, 2H), 6.75 (dd, J = 8.2 and 1.8 Hz, 1H), 6.97 (d, J = 8.2Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.28-7.46 (m, 11H), 7.96 (s, 1H), 10.20 (s, 1H).

MS (EI) m / z; 611 [M]$^+$ (bp).

【0134】合成例28

【0135】32 % 収率

黄色結晶

mp. 227-228 ° C

^{1}H-NMR (DMSO-d_6) δ: 1.15 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 2.90-3.10 (m, 4H), 3.25 (br s, 1H), 3.74 (s, 3H), 3.96 (q, J = 7.0 Hz, 2H), 4.00-4.05 (br s, 1H), 4.42 (br s, 1H), 6.45 (br s, 1H), 6.73 (dd, J = 8.4 and 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.92 (s, 1H), 10.16 (s, 1H).

MS (EI) m / z; 473 [M]$^+$, 233 (bp).

【0136】合成例29

【0137】40 % 収率

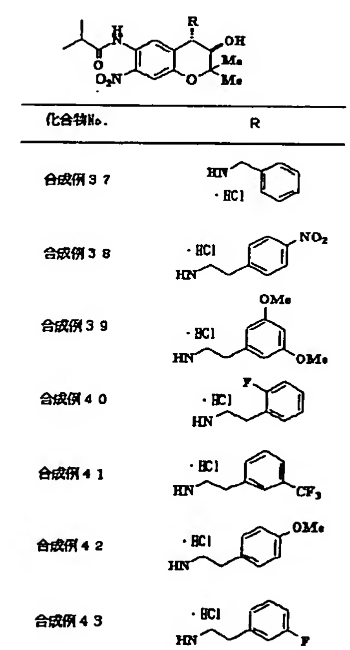
黄色非晶質

^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.91 (s, 3H),2.00 (s, 3H), 2.45-2.50 (m, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.75-2.85 (m,1H), 3.58 (dd, A part of AB, J = 9.6 and 5.3 Hz, 1H), 3.65 (d, B part of AB, J = 9.6 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 5.43 (d, J = 5.3 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H), 8.32 (s, 1H), 9.95 (s, 1H).

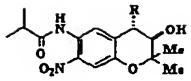
MS (EI) m / z; 443 [M]$^+$, 237 (bp).

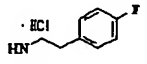
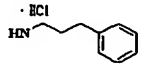
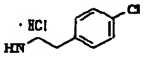
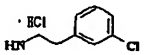
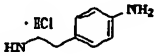
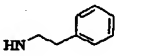
【0138】合成例30

【0139】98 % 収率
黄色結晶
mp. 214-216 ° C
MS (EI) m / z; 467 [M]+, 308 (bp).
【0140】合成例31
【0141】96 % 収率
橙色結晶
mp. 133-134 ° C
^{1}H-NMR (CDCl$_3$) δ: 1.18 (s, 3H), 1.49 (s, 3H), 1.60 (br s, 1H), 2.28 (s,3H), 2.75-3.00 (m, 5H), 3.50 (d, A part of AB, J = 10.2 Hz, 1H), 3.69 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.05-7.20 (m, 4H), 7.61 (s, 1H), 8.59 (s, 1H), 9.97 (s, 1H).
MS (EI) m / z; 433[M]+ (bp).
【0142】合成例32
【0143】82 % 収率
橙色固形物
^{1}H-NMR (CDCl$_3$) δ: 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.80-3.00 (m, 6H), 3.49 (d, A part of AB, J = 10.1 Hz, 1H), 3.69 (dd, B part of AB,J = 10.1 and 1.2 Hz, 1H), 7.40-7.50 (m, 4H), 7.62 (s, 1H), 8.63 (s, 1H),9.99 (s, 1H).
MS (EI) m / z; 467 [M]+, 348 (bp).
【0144】合成例33
【0145】84 % 収率
黄色非晶質
^{1}H-NMR (CDCl$_3$) δ: 1.19 (s, 3H), 1.49 (s, 3H), 1.58 (br s, 1H), 2.27 (s,3H), 2.80-2.98 (m, 3H), 3.08-3.23 (m, 2H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.72 (d, B part of AB, J = 10.3 Hz, 1H), 7.02-7.08 (m, 1H),7.25-7.28 (m, 2H), 7.61 (s, 1H), 8.68 (s, 1H), 10.00 (s, 1H).
MS (EI) m / z; 467 [M]+, 354 (bp).
【0146】合成例34
【0147】黄色結晶
mp. : 160.0-165.0 ° C
^{1}H-NMR (CDCl$_3$) δ: 1.33 (s, 3H), 1.53 (s, 3H), 2.14 (s, 3H), 2.61 (d, J =2.8 Hz, 1H), 3.79 (dd, J = 2.8, 8.8 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H),6.78 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8.0 Hz,2H), 7.66 (s, 1H), 8.59 (s, 1H), 9.79 (s, 1H).
MS (EI) m / z; 371[M]+, 299, 257 (bp).
【0148】合成例35
【0149】87 % 収率
黄色非晶質, ジアステレオマー1：1混合物.
^{1}H-NMR (CDCl$_3$) δ: 1.15 (s, 6H), 1.29 (d, J = 5.5 Hz, 6H), 1.45 (s, 3H),1.48 (s, 3 H), 2.28 (s, 3H), 2.29 (s, 3H), 2.58 (br s, 1H), 2.75-2.90 (m, 8H), 2.95 (br s, 1H), 3.37 (d, J = 10.0 Hz, 1H), 3.50 (d, J = 10.0 Hz,1H), 3.62 (d, J = 10.1 Hz, 1H), 3.64 (d, J = 10.1 Hz, 1H), 7.20-7.38 (m, 10H), 7.59 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H), 8.65 (s, 1H), 9.95 (s,1H), 10.00 (s, 1H).
MS (EI) m / z; 414[M+1]+, 279 (bp).
【0150】合成例36
【0151】27 % 収率
橙色固形物, ジアステレオマーA (more polar).
^{1}H-NMR (CDCl$_3$) δ: 1.20 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.44 (s, 3H),1.72 (br s, 2H), 2.26 (s, 3H), 2.61 (dd, A part of AB, J = 13.4 and 7.1Hz, 1H), 2.86 (dd, B part of AB, J = 13.4 and 6.5 Hz, 1H), 3.28-3.36 (m,1H), 3.34 (d, A part of AB, J = 9.7 Hz, 1H), 3.63 (dd, B part of AB, J= 9.7 and 1.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.60 (s, 1H), 8.84 (s, 1H), 10.06 (s, 1H).
MS (EI) m / z; 447 [M]+ (bp).
【0152】32 % 収率
黄色固形物, ジアステレオマーB (less polar).
^{1}H-NMR (CDCl$_3$) δ: 1.14 (d, J = 6.0 Hz, 3H), 1.23 (s, 3H), 1.49 (s, 3H),1.60 (br s, 2H), 2.29 (s, 3H), 2.76 (d, J = 6.8 Hz, 2H), 3.52 (d, A partof AB, J = 10.0 Hz, 1H), 3.51 (dq, J = 6.8 and 6.0 Hz, 1H), 3.65 (dd, Bpart of AB, J = 10.0 and 1.0 Hz, 1H), 7.25 (s, 4H), 7.56 (s, 1H), 8.54(s, 1H), 9.91 (s, 1H).
MS (EI) m / z; 447 [M]+ (bp).
【0153】合成例37〜49
【0154】
【化24】



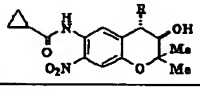
【0155】
【化25】

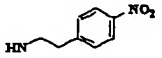
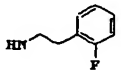
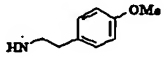
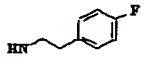
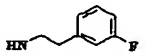
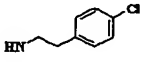


化合物No.	R
合成例44	
合成例45	
合成例46	
合成例47	
合成例49	
合成例49	

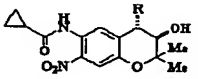
【0156】合成例37～49における一般合成法
【0157】6－イソプロピルアミド－3，4－エポキシ－3，4－ジヒドロ－2，2－ジメチル－7－ニトロ－2H－1－ベンゾピラン（200 mg，0.65 mmol）、臭化リチウム（226mg，2.6 mmol）のテトラヒドロフラン溶液（2 mL）に室温でアミン(1.31 mmol)を加え、65 ℃で 4 時間撹拌した。酢酸エチルを加え、有機相を飽和食塩水で2回洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残査をシリカゲルカラムクロマトグラフィーで精製し目的物を粗物として得た。続いて目的物のメタノール溶液（10 倍量）に氷冷下、10 % 塩化水素－メタノール溶液（2 倍量)を加え 30 分間撹拌した。ジイソプロピルエーテル（100 倍量)を加え、得られた結晶を沪取、ジイソプロピルエーテルで洗浄し、目的物の塩酸塩を得た。得られた塩酸塩を酢酸エチル，飽和炭酸水素ナトリウム水溶液で抽出後，^{1}H-NMRを測定した。
【0158】合成例37
【0159】33 % 収率
黄色結晶
mp. : 228 ° C (decomp).
MS (FAB) m / z; 414[M+H]$^+$.
【0160】合成例38
【0161】30 % 収率
黄色結晶
mp. : 257 ° C (decomp).
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.32 (d, J = 6.8 Hz, 6 H), 1.49 (s, 3H),1.60 (br s, 1H), 2.65 (quint, J = 6.8 Hz, 1H), 2.80 (br s, 1H), 2.95-3.05 (m, 4H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part ofAB, J = 10.3 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 8.17 (d, J= 8.4 Hz, 2H), 8.74 (s, 1H), 10.18 (s, 1H).
MS (FAB) m / z; 473 [M+H]$^+$.
【0162】合成例39
【0163】33 % 収率
黄色結晶
mp. : 244-245 ° C (decomp).
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H), 1.48 (s, 3H),1.60 (br s,1H), 2.63 (quint, J = 6.8 Hz, 1H), 2.77 (t, J = 6.8 Hz, 2H),2.95-3.00 (m, 3H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part of AB, J = 10.3 Hz, 1H), 3.78 (s, 6H), 6.32 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 2H), 7.62 (s, 1H), 8.71 (s, 1H), 10.14 (s, 1H).
MS (FAB) m / z; 488 [M+H]$^+$.
【0164】合成例40
【0165】46 % 収率
黄色結晶
mp. : 239 ° C (decomp).
MS (FAB) m / z; 446 [M+H]$^+$.
【0166】合成例41
【0167】38 % 収率
黄色結晶
mp. : 249 ° C (decomp).
MS (FAB) m / z; 496 [M+H]$^+$.
【0168】合成例42
【0169】23 % 収率
黄色結晶
mp. : 228 ° C (decomp).
MS (FAB) m / z; 458 [M+H]$^+$.
【0170】合成例43
【0171】31 % 収率
黄色結晶
mp. : 243 ° C (decomp).
MS (FAB) m / z; 446 [M+H]$^+$.
【0172】合成例44
【0173】26 % 収率
黄色結晶
mp. : 242 ° C (decomp).
^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.31 (d, J = 6.9 Hz, 6H), 1.48 (s, 3H),2.00 (br s, 2H), 2.64 (quint, J = 6.9Hz, 1H), 2.75-3.00 (m, 4H), 3.50 (d, A part of AB, J = 10.0 Hz, 1H), 3.69 (d, B part of AB, J = 10.0 Hz, 1H), 7.01 (t, J = 8.5 Hz, 2H), 7.15-7.26 (m, 2H), 7.63 (s, 1H), 8.69 (s, 1H), 10.15 (s, 1H).
MS (FAB) m / z; 446 [M+H]$^+$.
【0174】合成例45
【0175】9 % 収率
黄色結晶

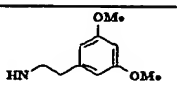
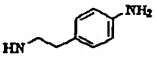
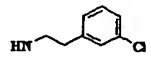
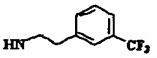
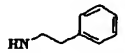
mp. : 112-116 ° C (decomp).
MS (FAB) m / z; 442 [M+H]⁺.
【0176】合成例46
【0177】24 % 収率
黄色結晶
mp. : 250 ° C (decomp).
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.32 (d, J = 7.0 Hz, 6H), 1.49 (s, 3H), 1.62 (br s, 2H), 2.65 (quint, J = 7.0 Hz, 1H), 2.81 (t, J = 6.6 Hz, 2H), 2.88-3.00 (m, 2H), 3.48 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, Bpart of AB, J = 10.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3Hz, 2H), 7.63 (s, 1H), 8.71 (s, 1H), 10.16 (s, 1H).
MS (FAB) m / z; 462 [M+H]⁺.
【0178】合成例47
【0179】35 % 収率
黄色結晶
mp. : 249 ° C (decomp).
MS (FAB) m / z; 462 [M+H]⁺.
【0180】合成例48
【0181】16 % 収率
黄色結晶
mp. : 204-208 ° C (decomp).
MS (FAB) m / z; 443 [M+H]⁺.
【0182】合成例49
【0183】赤色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.32 (d, J = 7.0 Hz, 6H), 1.48 (s, 3H), 2.27 (s, 3H), 2.65 (q, J = 7.0 Hz, 1H), 2.86-2.98 (m, 4H), 3.46 (d, J =10.0 Hz, 1H), 3.68 (d, J = 10.0 Hz, 1H), 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.63 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 420[M+1]⁺, 344, 179 (bp).
【0184】合成例50～75
【0185】
【化26】



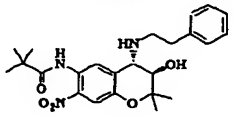
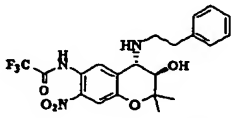
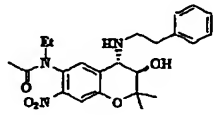
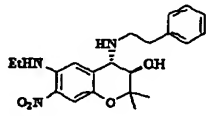
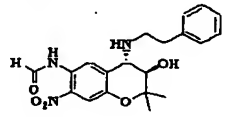
化合物No.	R
合成例50	
合成例51	
合成例52	
合成例53	
合成例54	
合成例55	
合成例56	

【0186】
【化27】

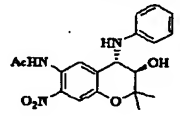
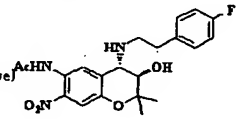
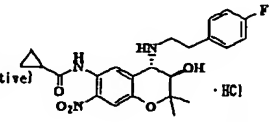
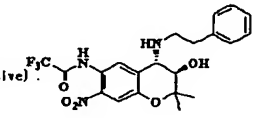


化合物No.	R
合成例57	
合成例58	
合成例59	
合成例60	
合成例61	
合成例62	

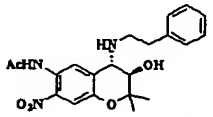
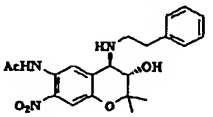
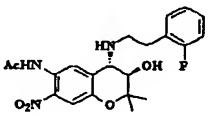
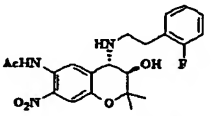
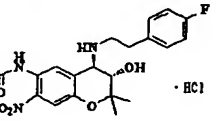
【0187】
【化28】

化合物No.	構造式
合成例63	
合成例64	
合成例65	
合成例66	
合成例67	

【0188】
【化29】

化合物No.	構造式
合成例68 (optically active)	
合成例69 (optically active)	
合成例70 (optically active)	
合成例71 (optically active)	

【0189】
【化30】

化合物No.	構造式
合成例72 (optically active)	
合成例73 (optically active)	
合成例74 (optically active)	
合成例75 (optically active)	
合成例76 (optically active)	

【0190】合成例50～75における一般合成法
【0191】6-シクロプロピルアミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン (200 mg, 0.66 mmol)、臭化リチウム (226mg, 2.6 mmol) のテトラヒドロフラン溶液 (2 mL) に室温で、アミン(1.31 mmol) を加え、65 ℃で 4時間撹拌した。酢酸エチルを加え、有機層を飽和食塩水で2回洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残査をシリカゲルカラムクロマトグラフィーで精製し目的物を得た。
【0192】合成例50
【0193】収率 30%
^{1}H-NMR ($CDCl_3$) δ: 0.96-0.98 (m, 2H), 1.10-1.78 (m, 5H), 1.48 (s, 3H), 1.63-1.66 (m, 1H), 2.93-3.01 (m, 4H), 3.52 (d, J =10.1 Hz, 1H), 6.68 (d, J=10.1 Hz, 1H), 7.40-7.42 (m, 2H), 7.63 (s, 1H), 8.14-8.17 (m, 2H), 8.66(s, 1H), 10.29 (bs, 1H).
MS (EI) m / z; 334 (bp), 471 $[M]^+$.
【0194】合成例51
【0195】収率 38%
^{1}H-NMR ($CDCl_3$) δ: 0.92-0.95 (m, 2H), 1.09-1.13 (m, 2H), 1.19 (s, 3H), 1.50 (s, 3H), 1.63-1.64 (m, 1H), 1.80-1.84 (m, 2H), 2.58-2.68 (m, 4H), 3.56 (d, J =10.1 Hz, 1H), 3.71 (dd, J =0.9, 10.1 Hz, 1H), 7.14-7.27 (m, 5H), 7.61 (s, 1H), 8.72 (d, J =0.9 Hz, 1H), 10.30 (bs, 1H).
MS (EI) m / z; 300 (bp), 439 $[M]^+$.
【0196】合成例52
【0197】収率 71%
^{1}H-NMR ($CDCl_3$) δ: 0.94-0.96 (m, 2H), 1.10-1.17 (m,

5H), 1.47 (s, 3H), 1.63-1.66 (m, 1H), 2.81-2.94 (m, 4H), 3.50 (d, J =10.1 Hz, 1H), 3.70 (d, J=10.1 Hz, 1H), 6.96-7.22 (m, 4H), 7.60 (s, 1H), 8.64 (s, 1H), 10.25 (bs, 1H).
MS (EI) m / z; 303 (bp), 443 [M]+.
【0198】合成例53
【0199】収率 47%
^{1}H-NMR ($CDCl_3$) δ: 0.93-0.96 (m, 2H), 1.10-1.17 (m, 5H), 1.48 (s, 3H), 1.63-1.65 (m, 1H), 2.72-2.89 (m, 4H), 3.50 (d, J =10.1 Hz, 1H), 3.67 (dd,J =0.7, 10.1 Hz, 1H), 3.77 (s, 3H), 6.80-6.82 (m, 2H), 7.10-7.13 (m, 2H), 7.60 (s, 1H), 8.63 (s, 1H), 10.25 (bs, 1H).
MS (FAB) m / z; 121, 456 [M+1]+.
【0200】合成例54
【0201】収率 54%
^{1}H-NMR ($CDCl_3$) δ: 0.95-0.97 (m, 2H), 1.10-1.17 (m, 2H), 1.26 (s, 3H), 1.48 (s, 3H), 1.63-1.67 (m, 1H), 2.76-2.94 (m, 4H), 3.50 (d, J =10.2 Hz, 1H), 3.67 (dd, J =1.0, 10.2 Hz, 1H), 6.94-6.99 (m, 2H), 7.15-7.26 (m, 2H), 7.61 (s, 1H), 8.61 (d, J =1.0 Hz, 1H), 10.26 (bs, 1H).
MS (EI) m / z; 260 (bp), 443 [M]+.
【0202】合成例55
【0203】収率 53%
^{1}H-NMR ($CDCl_3$) δ: 0.94-0.97 (m, 2H), 1.11-1.17 (m, 5H), 1.48 (s, 3H), 1.63-1.65 (m, 1H), 2.79-2.94 (m, 4H), 3.49 (d, J =10.3 Hz, 1H), 3.67 (dd,J =0.9, 10.3 Hz, 1H), 6.90-7.01 (m, 3H), 7.23-7.26 (m, 1H), 7.62 (s, 1H), 8.63 (d, J =0.9 Hz, 1H), 10.27 (bs, 1H).
MS (EI) m / z; 301 (bp), 443 [M]+.
【0204】合成例56
【0205】収率 58%
^{1}H-NMR ($CDCl_3$) δ: 0.87-0.90 (m, 2H), 1.11-1.14 (m, 2H), 1.17 (s, 3H), 1.48 (s, 3H), 1.63-1.67 (m, 1H), 2.77-2.81 (m, 2H), 2.89-2.93 (m, 2H), 3.48 (d, J =10.3 Hz, 1H), 3.65 (d, J =10.3 Hz, 1H), 7.16-7.26 (m, 4H), 7.62(s, 1H), 8.65 (s, 1H), 10.28 (bs, 1H).
MS (EI) m / z; 305 (bp), 460 [M]+.
【0206】合成例57
【0207】収率 56%
^{1}H-NMR ($CDCl_3$) δ: 0.92-0.95 (m, 2H), 1.09-1.18 (m, 5H), 1.49 (s, 3H), 1.62-1.65 (m, 1H), 2.73-2.92 (m, 4H), 3.51 (d, J =10.2Hz, 1H), 3.67 (d, J=10.2 Hz, 1H), 3.77 (s, 6H), 6.31 (s, 3H), 6.37 (s, 2H), 7.61 (s, 1H), 8.64 (s, 1H), 10.26 (bs, 1H).
MS (EI) m / z; 470 (bp), 486 [M]+.
【0208】合成例58
【0209】収率 52%
^{1}H-NMR ($CDCl_3$) δ: 0.92-0.97 (m, 2H), 1.10-1.16 (m, 2H), 1.20 (s, 3H), 1.51 (s, 3H), 1.63-1.68 (m, 1H), 3.64 (d, J =10.1 Hz, 1H), 3.77-3.84 (m, 3H), 7.25-7.39 (m, 5H), 7.67 (s, 1H), 8.88 (s, 1H), 10.34 (bs, 1H).
MS (EI) m / z; 339 (bp), 411 [M]+.
【0210】合成例59
【0211】収率 57%
^{1}H-NMR ($CDCl_3$) δ: 0.93-0.96 (m, 2H), 1.11-1.17 (m, 5H), 1.47 (s, 3H), 1.63-1.65 (m, 1H), 2.68-2.71 (m, 2H), 2.85-2.88 (m, 2H), 3.46 (d, J =10.1Hz, 1H), 3.64 (d, J =10.1 Hz, 1H), 6.62-6.64 (m, 2H), 6.70-7.02 (m, 2H),7.61 (s, 1H), 8.64 (s, 1H), 10.26 (bs, 1H).
MS (EI) m / z; 333 (bp), 439 [M]+.
【0212】合成例60
【0213】収率 42%
^{1}H-NMR ($CDCl_3$) δ: 0.94-0.97 (m, 2H), 1.12-1.17 (m, 5H), 1.49 (s, 3H), 1.63-1.67 (m, 1H), 2.77-2.94 (m, 4H), 3.49 (d, J =10.3 Hz, 1H), 3.67 (dd,J =0.9, 10.3 Hz, 1H), 7.10-7.22 (m, 4H), 7.62 (s, 1H), 8.63 (d, J =0.9 Hz, 1H), 10.27 (bs, 1H).
MS (EI) m / z; 334 (bp), 460 [M]+.
【0214】合成例61
【0215】収率 61%
^{1}H-NMR ($CDCl_3$) δ: 0.94-0.97 (m, 2H), 1.10-1.18 (m, 5H), 1.48 (s, 3H), 1.63-1.66 (m, 1H), 2.85-2.96 (m, 4H), 3.53 (d, J =10.1 Hz, 1H), 3.71 (d, J=10.1 Hz, 1H), 7.28-7.46 (m, 4H), 7.60 (s, 1H), 8.66 (s, 1H), 10.26 (bs, 1H).
MS (EI) m / z; 259 (bp), 494 [M]+.
【0216】合成例62
【0217】赤色非晶質
^{1}H-NMR ($CDCl_3$) δ: 0.94-0.97 (m, 2H), 1.12-1.15 (m, 2H), 1.16 (s, 3H), 1.47 (s, 3H), 1.61-1.67 (m, 1H), 2.79-2.96 (m, 4H), 3.45 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 9.9 Hz, 1H), 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.62 (s,1H), 10.26 (s, 1H)
MS (EI) m / z; 418[M+1]+, 346, 309, 179 (bp).
【0218】合成例63
【0219】赤色結晶
mp. : 169.0-170.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.37 (s, 9H), 1.47 (s, 3H), 2.81-2.85 (m, 2H), 2.93-2.97 (m, 2H), 3.47 (d, J = 10.1 Hz, 1H), 3.67 (d, J = 10.1 Hz, 1H), 7.19-7.32 (m, 5H), 7.63 (s, 1H), 8.74 (s, 1H), 10.44 (s, 1H).
MS (EI) m / z; 441[M+1]+, 322, 268 (bp).
【0220】合成例64

【0221】赤色結晶
mp. : 176.5-178.0 ° C
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.54 (s, 3H), 3.05-3.16 (m, 3H), 3.26-3.30 (m, 1H), 4.06 (d, J = 8.6 Hz, 1H), 4.58 (d, J = 8.6 Hz, 1H), 7.15-7.26 (m, 5H), 7.73 (s, 1H), 8.65 (s, 1H), 10.66 (s, 1H).
MS (EI) m / z; 453[M]$^+$ (bp).
【0222】合成例65
【0223】赤色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.02 (t, J = 6.8 Hz, 3H), 1.24 (s, 3H), 1.52 (s, 3H),1.83 (s, 3H), 2.68-2.96 (m, 4H), 3.33 (q, J = 6.8 Hz, 1H), 3.63 (d, J =10.1 Hz, 1H), 3.74 (d, J = 10.1 Hz, 1H), 3.77-3.90 (m, 1H), 7.19-7.39 (m, 7H).
MS (FAB) m / z; 428[M]$^+$ (bp), 268, 105.
【0224】合成例66
【0225】赤色非晶質
^{1}H-NMR ($CDCl_3$) δ: 1.15 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.46 (s, 3H),2.82-2.86 (m, 3H), 2.91-2.96 (m, 1H), 3.08-3.13 (m, 2H), 3.59 (d, J = 10.1 Hz, 1H), 3.65 (d, J = 10.1 Hz, 1H), 6.58 (s, 1H), 7.22-7.26 (m, 3H),7.31-7.34 (m, 2H), 7.53 (brs, 1H), 7.60 (s, 1H),
MS (EI) m / z; 385[M]$^+$, 314, 266, 223 (bp).
【0226】合成例67
【0227】黄色油状物
^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.48 (s, 3H), 2.75-3.00 (m, 6H), 3.52 (d, A part of AB, J = 9.9 Hz, 1H), 3.70 (d, B part of AB, J = 9.9 Hz, 1H),7.18-7.35 (m, 5H), 7.62 (s, 1H), 8.45 (s, 1H), 8.66 (s, 1H), 9.98 (s, 1H).
MS (EI) m / z; 385[M]$^+$, 313 (bp).
【0228】合成例68
【0229】(+)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
黄色非晶質
[α] $^{26}_D$ +104.6 (c 0.64, EtOH)
【0230】合成例69
【0231】(+)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
黄色結晶
(HCl salt): mp. 246-247 ° C (decomp).
(HCl salt): [α]$_D^{26}$ -71.8 (c 0.38, EtOH)
【0232】合成例70
【0233】(+)-(3R*, 4R*)-3, 4-エポキシ-6-シクロプロピルアミド-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
(HCl salt): 黄色結晶
(HCl salt): mp. 241-246 ° C (decomp).
(HCl salt): [α] $^{26}_D$ -92.1 (c 0.45, EtOH)
【0234】合成例71
【0235】(+)-(3R*, 4R*)-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-6-トリフルオロアセタミド-2H-1-ベンゾピラン(99% ee 以上)から誘導
(HCl salt): 黄色結晶
(HCl salt): mp. 243 ° C (decomp).
[α] $^{26}_D$ -54.8 (c 0.5, EtOH)
【0236】合成例72
(+)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
赤色非晶質
[α] $^{26}_D$ -64.3 (c 1.03, EtOH)
【0237】合成例73
【0238】(-)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
赤色非晶質
[α] $^{26}_D$ +61.2 (c 0.98, EtOH)
【0239】合成例74
【0240】(+)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
赤色非晶質
[α] $^{26}_D$ -64.6 (c 1.00, EtOH)
【0241】合成例75
【0242】(-)-(3R*, 4R*)-6-アセタミド-3, 4-エポキシ-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン(99% ee 以上)から誘導
赤色非晶質
[α] $^{26}_D$ +60.8 (c 0.93, EtOH)
【0243】合成例76
(+)-(3R*, 4R*)-3, 4-エポキシ-6-イソプロピルアミド-3, 4-ジヒドロ-2, 2-ジメチル-7-ニトロ-2H-1-ベンゾピラン (1.0 g, 3.59 mmol)、臭化リチウム (1.24 g, 14.36 mmol) のアセトニトリル溶液 (10 mL) に室温で それぞれ4位置換基に相当する4-フルオロフェネチルアミン (1.88 mL, 14.4 mmol) を加え、65 ℃で 2 時間撹拌した。酢酸エチルを加え、有機相を飽和炭酸水素ナトリウム溶液、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残査をシリカゲルカラムクロマトグラフィーで精製し4位アミン置換体を得た。続いて、4位アミン置換体のエタノール溶液 (10 倍量) に室温で濃塩酸 (6 当量) を加え 90 ° C で 1 日加熱還流した。飽和炭酸水素ナトリウム溶液を加え酢酸エチルで抽出、有機相を飽和食塩水で1 回洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去して4位アミン置換体の6位脱アミド体を得

た。続いて６位脱アミド体のジメチルホルムアミド溶液（20 倍量）に室温で 4 規定塩化水素－ジオキサン溶液（1.4 当量）を加え、10 分間撹拌した。６位置換基に対応する酸クロリド（1.5 当量）を滴下して 1 時間撹拌、続いてメタノール(1 mL）を加えさらに 10 分間撹拌した。水を加え、酢酸エチルで抽出、有機相を飽和炭酸水素ナトリウム溶液、飽和食塩水で洗浄し、無水硫酸マグネシウムで乾燥した。溶媒を留去後、残査をシリカゲルカラムクロマトグラフィーで精製し目的物を得た。続いて目的物のメタノール溶液（10 倍量）に氷冷下、10 % 塩化水素－メタノール溶液（2 倍量）を加え 30 分間撹拌した。ジイソプロピルエーテル（100 倍量）を加え、得られた結晶を沪取、ジイソプロピルエーテルで洗浄し、目的物の塩酸塩を得た。

【０２４４】黄色結晶

mp. : 244-245 ° C (decomp).

〔α〕$^{26}_{D}$ -67.3 (c 0.4, EtOH)

【０２４５】〔製剤例〕

【０２４６】製剤例１

錠剤

本発明化合物	１０ｇ
乳　　糖	２６０ｇ
微結晶セルロース	６００ｇ
コーンスターチ	３５０ｇ
ヒドロキシプロピルセルロース	１００ｇ
ＣＭＣ－Ｃａ	１５０ｇ
ステアリン酸マグネシウム	３０ｇ
全　　量	１，５００ｇ

上記成分を常法により混合したのち１錠中に１ｍｇの活性成分を含有する糖衣錠１０，０００錠を製造する。

【０２４７】製剤例２

カプセル剤

本発明化合物	１０ｇ
乳　　糖	４４０ｇ
微結晶セルロース	１，０００ｇ
ステアリン酸マグネシウム	５０ｇ
全　　量	１，５００ｇ

上記成分を常法により混合したのちゼラチンカプセルに充填し、１カプセル中に１ｍｇの活性成分を含有するカプセル剤１０，０００カプセルを製造する。

【０２４８】製剤例３

軟カプセル剤

本発明化合物	１０ｇ
ＰＥＧ４００	４７９ｇ
飽和脂肪酸トリグリセライド	１，５００ｇ
ハッカ油	１ｇ
ポリソルベート(Polysorbate)80	１０ｇ
全　　量	２，０００ｇ

上記成分を混合したのち常法により３号軟ゼラチンカプセルに充填し、１カプセル中に１ｍｇの活性成分を含有する軟カプセル剤１０，０００カプセルを製造する。

【０２４９】製剤例４

軟膏

本発明化合物	１．０ｇ
流動パラフィン	１０．０ｇ
セタノール	２０．０ｇ
白色ワセリン	６８．４ｇ
エチルパラベン	０．１ｇ
１－メントール	０．５ｇ
全　　量	１００．０ｇ

上記成分を常法により混合し、１％軟膏とする。

【０２５０】製剤例５

坐剤

本発明化合物	１ｇ
ウィッテップゾールＨ１５＊	４７８ｇ
ウィッテップゾールＷ３５＊	５２０ｇ
ポリソルベート(Polysorbate)80	１ｇ
全　　量	１，０００ｇ

「＊　トリグリセライド系化合物の商標名

ウィッテップゾール＝Ｗｉｔｅｐｓｏｌ」

上記成分を常法により溶融混合し、坐剤コンテナーに注ぎ冷却固化して１ｍｇの活性成分を含有する１ｇ坐剤１，０００個を製造する。

【０２５１】製剤例６

注射剤

本発明化合物	１ｍｇ
注射用蒸留水	５ｍＬ

用時、溶解して用いる。

【０２５２】〔薬理試験例〕左心房筋および右心室乳頭筋における不応期に及ぼす影響

試験方法

モルモットより心臓を摘出し，95%O_2+5%CO_2を通気したKrebs-Henseleit溶液中にて，左心房あるいは右心室乳頭筋を分離した。標本は，電気刺激装置を用いて，1Hz，刺激に反応する閾値の1.5倍の電圧で刺激（基本的な刺激；Ｓ１）し，その時発生する収縮をFDピックアップ，歪圧力アンプを介して熱ペンレコーダーに記録した。不応期は，測定可能な収縮が結果として生じるＳ１および特別な刺激（Ｓ２）の間の最も小さな間隔として定義した。Ｓ１とＳ２の間隔は左心房筋標本では150m秒から開始し，100m秒までは10m秒ずつ，その後は5m秒ずつ不応期に至るまで短縮させ，右心室乳頭筋標本では300m秒から開始し，10m秒ずつ不応期に至るまで短縮させた。なお，Ｓ２は刺激に反応する閾値の2倍に設定した。実験温度は，36±1℃とした。なお，溶媒は，左心房筋および右心室乳頭筋いずれの不応期にも影響しなかった。化合物を添加する前の基本的な値を測定後，化合物を累積的に添加して，各濃度15分間インキュベーションした後に不応期を測定した。

【０２５３】結果

本発明に係わる化合物は，心房に対して強力な不応期延長作用を示した。

【0254】

【表1】

化合物(合成例No.)	不応期延長 EC_{20} (μM)	化合物(合成例No.)	不応期延長 EC_{20} (μM)
1	6.1	5	5.5
3	4.0	6	1.4
4	5.0	8	1.8

【0255】

【発明の効果】本発明化合物は、不応期延長作用を示し、不整脈の改善に有用である。従って、本発明は、有用な不整脈治療剤を提供することができる。

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